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 NEWS 34 Apr 21 New current-awareness alert (SDI) frequency in
          WPIDS/WPINDEX/WPIX
 NEWS 35 Apr 28 RDISCLOSURE now available on STN
 NEWS 36 May 05 Pharmacokinetic information and systematic chemical names
          added to PHAR
 NEWS 37 May 15 MEDLINE file segment of TOXCENTER reloaded
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=> s PKDL2 or ADPKD or autosomal polycystic kidney disease
L1      1777 PKDL2 OR ADPKD OR AUTOSOMAL POLYCYSTIC KIDNEY
DISEASE

=> s l1 and (transgen? or knockout or disrupt? or deficien?)
L2      114 L1 AND (TRANSGEN? OR KNOCKOUT OR DISRUPT? OR
DEFICIEN?)

=> s PKDL2
L3        1 PKDL2

=> dup rem l2
PROCESSING COMPLETED FOR L2
L4       56 DUP REM L2 (58 DUPLICATES REMOVED)

=> d bib abs 1-
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L4  ANSWER 1 OF 56  CAPLUS  COPYRIGHT 2003 ACS
AN  2002:449426  CAPLUS
DN  137:28988
TI  ***Transgenic*** mice containing polycystin-2 ***PKDL2*** gene
    ***disruption*** and the uses the mice as disease model for drug
    screening
IN  Allen, Keith D.
PA  Deltagen, Inc., USA
SO  PCT Int. Appl., 50 pp.
    CODEN: PIXXD2
DT  Patent
LA  English
FAN.CNT 1
    PATENT NO.      KIND  DATE        APPLICATION NO.  DATE
    --------------- ----  ----------  ---------------  --------
PI  WO 2002045492   A2  20020613    WO 2001-US46478  20011204
    WO 2002045492   C1  20020926
        W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
           CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
           GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
           LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
           PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
           UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
           CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
           BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
    AU 2002027220   A5  20020618    AU 2002-27220   20011204
    US 2002194636   A1  20021219    US 2001-5211    20011204
PRAI US 2000-250999P  P  20001204
    US 2000-256201P  P  20001213
    WO 2001-US46478  W  20011204
AB  The present invention relates to ***transgenic*** animals, as well as
    compns. and methods relating to the characterization of gene function.
    Specifically, the present invention provides ***transgenic*** mice
    comprising mutations in a polycystin-2 ***PKDL2*** gene. The DNA and
    protein sequences of ***PKDL2*** from mouse were disclosed and the
    ***PKDL2*** DNA sequence was used for design the targeting arms for gene
    knocking out. The resulted ***transgenic*** mouse exhibits a
    phenotype of hyperactivity characterized by increased total distance
    traveled in an open field test. Such ***transgenic*** mice are useful
    as models for disease and for identifying agents that modulate gene
    expression and gene function, and as potential treatments for various
    disease states and disease conditions.

L4  ANSWER 2 OF 56  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS
INC.DUPLICATE
    1
AN  2003:94321  BIOSIS
DN  PREV200300094321
TI  Cleavage of polycystin-1 requires the receptor for egg jelly domain and is
    ***disrupted*** by human autosomal-dominant polycystic kidney disease
    1-associated mutations.
AU  Qian, Feng; Boletta, Alessandra; Bhunia, Anil K.; Xu, Hangxue; Liu,
    Lijuan; Ahrabi, Ali K.; Watnick, Terry J.; Zhou, Fang; Germino, Gregory G.
    (1)
CS  (1) Division of Nephrology, Johns Hopkins University School of Medicine,
    720 Rutland Avenue, Ross 958, Baltimore, MD, 21205, USA:
ggermino@jhmi.edu
    USA
SO  Proceedings of the National Academy of Sciences of the United States of
    America, (December 24 2002) Vol. 99, No. 26, pp. 16981-16986. print.
    ISSN: 0027-8424.
DT  Article
LA  English
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AB Polycystin-1 plays an essential role in renal tubular morphogenesis, and ***disruption*** of its function causes cystogenesis in human autosomal-dominant polycystic kidney disease (***ADPKD***). We demonstrated that polycystin-1 undergoes cleavage at G protein coupled receptor proteolytic site in a process that requires the receptor for egg jelly domain. Most of the N-terminal fragment remains tethered at the cell surface, although a small amount is secreted. PKD1-associated mutations in the receptor for egg jelly domain ***disrupt*** cleavage, abolish the ability of polycystin-1 to activate signal transducer and activator of transcription-1, and induce tubulogenesis in vitro. We conclude that the cleavage of polycystin-1 is likely essential for its biologic activity.

L4 ANSWER 3 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:464721 BIOSIS
DN PREV200200464721
TI Trans-heterozygous Pkd1 and Pkd2 mutations modify expression of polycystic kidney disease.
AU Wu, Guanqing; Tian, Xin; Nishimura, Sayoko; Markowitz, Glen S.; D'Agati, Vivette; Park, Jong Hoon; Yao, Lili; Li, Li; Geng, Lin; Zhao, Hongyu; Edelmann, Winfried; Somlo, Stefan (1)
CS (1) Boyer Center for Molecular Medicine, Yale University School of Medicine, 295 Congress Avenue, New Haven, CT, 06519-1418: guanqing.wu@vanderbilt.edu, stefan.somlo@yale.edu USA
SO Human Molecular Genetics, (1 August, 2002) Vol. 11, No. 16, pp. 1845-1854. http://hmg.oupjournals.org/. print.
ISSN: 0964-6906.
DT Article
LA English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) occurs by germline mutation in PKD1 or PKD2. Evidence of homozygous inactivation of either gene in human cyst lining cells as well as in mouse ***knockout*** models strongly supports a two-hit mechanism for cyst formation. Discovery of trans-heterozygous mutations in PKD1 and PKD2 in a minority of human renal cysts has led to the proposal that such mutations also can play a role in cyst formation. In the current study, we investigated the role of trans-heterozygous mutations in mouse models of polycystic kidney disease. In Pkd1+/-, Pkd2+/- and Pkd1+/-:Pkd2+/- mice, the renal cystic lesion was mild and variable with no adverse effect on survival at 1 year. In keeping with the two-hit mechanism of cyst formation, approximately 70% of kidney cysts in Pkd2+/- mice exhibited uniform loss of polycystin-2 expression. Cystic disease in trans-heterozygous Pkd1+/-:Pkd2+/- mice, however, was notable for severity in excess of that predicted by a simple additive effect based on cyst formation in singly heterozygous mice. The data suggest a modifier role for the 'trans' polycystin gene in cystic kidney disease, and support a contribution from threshold effects to cyst formation and growth.

L4 ANSWER 4 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2002:297353 BIOSIS
DN PREV200200297353
TI A complete mutation screen of the ***ADPKD*** genes by DHPLC.
AU Rossetti, Sandro; Chauveau, Dominique; Walker, Denise; Saggar-Malik, Anand; Winearls, Christopher G.; Torres, Vicente E.; Harris, Peter C. (1)
CS (1) Mayo Clinic, 200 First Street SW, 760 Stabile Building, Rochester, MN, 55905: harris.peter@mayo.edu USA
SO Kidney International, (May, 2002) Vol. 61, No. 5, pp. 1588-1599. http://www.blackwell-science.com/ cgilib/bsinc.bin?Journal=kidney. print.
ISSN: 0085-2538.
DT Article
LA English
AB Background. Genetic analysis is a useful diagnostic tool in autosomal dominant polycystic kidney disease (***ADPKD***), especially when imaging results are equivocal. However, molecular diagnostics by direct mutation screening has proved difficult in this disorder due to genetic and allelic heterogeneity and complexity of the major locus, PKD1. Methods. A protocol was developed to specifically amplify the exons of PKD1 and PKD2 from genomic DNA as 150 to 450 bp amplicons. These fragments
were analyzed by the technique of denaturing high-performance liquid chromatography (DHPLC) using a Wave Fragment Analysis System (***Transgenomics***) to detect base-pair changes throughout both genes. DHPLC-detected changes were characterized by sequencing. Results. Cost effective and sensitive mutation screening of the entire coding regions of PKD1 and PKD2 by DHPLC was optimized. All base-pair mutations to these genes that we previously characterized were detected as an altered DHPLC profile. To assess this method for routine diagnostic use, samples from a cohort of 45 genetically uncharacterized ***ADPKD*** patients were analyzed. Twenty-nine definite mutations were detected, 26 PKD1, 3 PKD2 and a further five possible missense mutations were characterized leading to a maximal detection rate of 76%. A high level of polymorphism of PKD1 also was detected, with 71 different changes defined. The reproducibility of the DHPLC profile enabled the recognition of many common polymorphisms without the necessity for re-sequencing. Conclusions. DHPLC has been demonstrated to be an efficient and effective means for gene-based molecular diagnosis of ***ADPKD*** . Differentiating missense mutations and polymorphisms remains a challenge, but family-based segregation analysis is helpful.

L4 ANSWER 5 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2002:400031 BIOSIS
DN PREV200200400031
TI The ion channel polycystin-2 is required for left-right axis determination in mice.
AU Pennekamp, Petra; Karcher, Christina; Fischer, Anja; Schweickert, Axel; Skryabin, Boris; Horst, Juergen; Blum, Martin (1); Dworniczak, Bernd
CS (1) University of Stuttgart-Hohenheim, Institute of Zoology, 220, D-70593, Stuttgart: mblum@uni-hohenheim.de Germany
SO Current Biology, (June 4, 2002) Vol. 12, No. 11, pp. 938-943. http://www.current-biology.com/. print.
ISSN: 0960-9822.
DT Article
LA English
AB Generation of laterality depends on a pathway which involves the asymmetrically expressed genes nodal, Ebaf, Leftb, and Pitx2 (1-3). In mouse, node monocilia are required upstream of the nodal cascade (4). In chick and frog, gap junctions are essential prior to node/organizer formation (5, 6). It was hypothesized that differential activity of ion channels gives rise to unidirectional transfer through gap junctions, resulting in asymmetric gene expression (3, 6). PKD2, which if mutated causes autosomal dominant polycystic kidney disease (***ADPKD***) in humans, encodes the calcium release channel polycystin-2 (7-11). We have generated a ***knockout*** allele of Pkd2 in mouse. In addition to malformations described previously (12), homozygous mutant embryos showed right pulmonary isomerism, randomization of embryonic turning, heart looping, and abdominal situs. Leftb and nodal were not expressed in the left lateral plate mesoderm (LPM), and Ebaf was absent from floorplate. Pitx2 was bilaterally expressed in posterior LPM but absent anteriorly. Pkd2 was ubiquitously expressed at headfold and early somite stages, with higher levels in floorplate and notochord. The embryonic midline, however, was present, and normal levels of Foxa2 and shh were expressed, suggesting that polycystin-2 acts downstream or in parallel to shh and upstream of the nodal cascade.

L4 ANSWER 6 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2002:341727 BIOSIS
DN PREV200200341727
TI Molecular basis of autosomal-dominant polycystic kidney disease.
AU Gallagher, A. R.; Hidaka, S.; Gretz, N.; Witzgall, R. (1)
CS (1) Institute for Anatomy and Cell Biology, University of Heidelberg, Im Neuenheimer Feld 307, 69120, Heidelberg: ralph.witzgall@urz.uni-heidelberg.de Germany
SO CMLS Cellular and Molecular Life Sciences, (April, 2002) Vol. 59, No. 4, pp. 682-693. http://www.birkhauser.ch/journals/1800/1800_tit.htm. print.
ISSN: 1420-682X.
DT Article; General Review
LA English
AB Autosomal-dominant polycystic kidney disease (***ADPKD***) is one of the most common monogenetic diseases in humans. The discovery that mutations in the PKD1 and PKD2 genes are responsible for ***ADPKD*** has sparked extensive research efforts into the physiological and pathogenetic role of polycystin-1 and polycystin-2, the proteins encoded by these two genes. While polycystin-1 may mediate the contact among cells or between cells and the extracellular matrix, a lot of evidence suggests that polycystin-2 represents an endoplasmic reticulum-bound cation channel. Cyst development has been compared to the growth of benign tumors and this view is highlighted by the model that a somatic mutation in addition to the germline mutation is responsible for cystogenesis (two-hit model of cyst formation). Since in vitro polycystin-1 and polycystin-2 interact through their COOH termini, the two proteins possibly act in a common pathway, which controls the width of renal tubules. The loss of one protein may lead to a ***disruption*** of this pathway and to the uncontrolled expansion of tubules. Our increasing knowledge of the molecular events in ***ADPKD*** has also started to be useful in designing novel diagnostic and therapeutic strategies.

L4 ANSWER 7 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002339839 EMBASE
TI Do polycystins function as cation channels?.
AU Ikeda M.; Guggino W.B.
CS W.B. Guggino, Department of Physiology, School of Medicine, Johns Hopkins University, 725 N. Wolfe St, Baltimore, MD 21205, United States. wguggino@jhmi.edu
SO Current Opinion in Nephrology and Hypertension, (2002) 11/5 (539-545). Refs: 36
ISSN: 1062-4821 CODEN: CNHYEM
CY United Kingdom
DT Journal; General Review
FS 022 Human Genetics
028 Urology and Nephrology
029 Clinical Biochemistry
LA English
SL English
AB Purpose of review: During the past 2 years growing evidence has emerged that polycystins (polycystin-1 and polycystin-2) are ion channels or regulators of ion channels. This suggests that autosomal-dominant polycystic kidney disease (***ADPKD***), which arises from mutations in polycystins, is a form of ion-channel disease (channelopathy). The

present review addresses the properties and the mode of action of polycystin channels; it also discusses how polycystin channel signaling may be involved in cyst formation in ***ADPKD*** . Recent findings: The precise functions of polycystin-1 and polycystin-2 are unclear. However, recent work has revealed that polycystin-1 may induce or modulate ion channels, including polycystin-2 channels, and that polycystin-2 functions as a calcium-regulated, calcium-permeable cation channel on the endoplasmic reticulum or on the plasma membrane with polycystin-1. These data suggest that ion-channel signaling mediated by polycystins is important for tubule formation in kidney and that ***disrupted*** signaling results in cyst formation. Summary: ***ADPKD*** is a systemic hereditary disease that is characterized by renal and hepatic cysts, and results in end-stage renal failure in 50% of affected individuals. Most cases (>95%) are caused by genetic mutations in either the PKD1 or the PKD2 gene, or both, which encode polycystin-1 and polycystin-2, respectively. The present review provides a hint of how malfunction of polycystins may give rise to cysts, based on recent observations concerning polycystin channels. Polycystin channel signaling may prove to be an important new target for therapy of ***ADPKD*** . .COPYRGT. 2002 Lippincott Williams & Wilkins.

L4 ANSWER 8 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002209766 EMBASE
TI Chronic renal failure in a patient with Sotos syndrome due to autosomal dominant polycystic kidney disease.
AU Cefle K.; Yildiz A.; Palanduz S.; Ozturk S.; Ozbey N.; Kylycaslan I.; Colakoglu S.; Balci C.
CS Dr. S. Palanduz, Fevzi Pasa Caddesi, Testereci Sokak No 1 Daire 10, Istanbul 34320, Turkey
SO International Journal of Clinical Practice, (2002) 56/4 (316-318).
Refs: 24
ISSN: 1368-5031 CODEN: IJCPF
CY United Kingdom
DT Journal; Article
FS 008 Neurology and Neurosurgery
022 Human Genetics
028 Urology and Nephrology
LA English
SL English
AB Sotos syndrome is characterised by accelerated growth, acromegalic appearance, mental retardation and social maladjustment. Most cases are sporadic, but familial cases have also been reported. We report a case of Sotos syndrome presenting with chronic renal failure due to autosomal dominant polycystic kidney disease (***ADPKD***). Ultrasonographic examination of the patient, his father and other family members revealed polycystic kidneys. Renal failure was present only in the Sotos case, who also had considerably larger cysts than other family members. We suggest that the underlying mechanism responsible from the somatic overgrowth in Sotos syndrome may also be linked with the development of larger cysts and earlier onset of renal failure in ***ADPKD*** . Although Sotos syndrome has been associated with urological abnormalities, chronic renal failure is very rare. To our knowledge, Sotos syndrome associated with ***ADPKD*** has not been reported before.

L4 ANSWER 9 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:74065 BIOSIS
DN PREV200300074065
TI Autosomal dominant polycystic kidney disease: Clinical and genetic aspects.
AU Bogdanova, Nadja; Markoff, Arseni; Horst, Juergen (1)
CS (1) Institut fuer Humangenetik, UKM Muenster, Vesaliusweg 12-14, D-48149, Muenster, Germany: horstj@uni-muenster.de Germany
SO Kidney & Blood Pressure Research, (2002) Vol. 25, No. 5, pp. 265-283. print.
ISSN: 1420-4096.
DT Article
LA English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) is one of the most common inherited disorders in humans. It accounts for 8-10% of the cases of end-stage renal disease worldwide, thus representing a serious medical, economical and social problem. ***ADPKD*** is in fact a systemic disorder, characterized with the development of cysts in the ductal organs (mainly the kidneys and the liver), also with gastrointestinal and cardiovascular abnormalities. In the last decade there was significant progress in uncovering the genetic foundations and in understanding of the pathogenic mechanisms leading to the renal impairment. This review will retrace the current knowledge about the epidemiology, pathogenesis, genetics, genetic and clinical heterogeneity, diagnostics and treatment of ***ADPKD*** .

L4 ANSWER 10 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:567386 BIOSIS
DN PREV200200567386
TI Proteolytic cleavage of polycystin-1 requires the REJ domain and is ***disrupted*** in ***ADPKD*** .
AU Qian, Feng (1); Boletta, Alessandra (1); Bhunia, Anil K. (1); Ahrabi, Ali (1); Xu, Hangxue (1); Liu, Lijuan (1); Germino, Gregory G. (1)
CS (1) Medicine, Johns Hopkins University, Baltimore, MD USA
SO Journal of the American Society of Nephrology, (September, 2002) Vol. 13, No. Program and Abstracts Issue, pp. 106A. http://www.jasn.org/. print.
Meeting Info.: Meeting of the American Society of Nephrology Philadelphia, PA, USA October 30-November 04, 2002 American Society of Nephrology . ISSN: 1046-6673.
DT Conference
LA English

L4 ANSWER 11 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002233833 EMBASE
TI Recurrent fetal loss associated with bilineal inheritance of type 1 autosomal dominant polycystic kidney disease.
AU Paterson A.D.; Wang K.R.; Lupea D.; St. George-Hyslop P.; Pei Y.
CS Dr. Y. Pei, 200 Elizabeth St, Toronto, Ont. M5G 2C4, Canada. york.pei@uhn.on.ca
SO American Journal of Kidney Diseases, (2002) 40/1 (16-20).
Refs: 26
ISSN: 0272-6386 CODEN: AJKDDP
CY United States
DT Journal; Article
FS 010 Obstetrics and Gynecology
022 Human Genetics
028 Urology and Nephrology
LA English
SL English
AB Background: Autosomal dominant polycystic kidney disease (***ADPKD***) is a common Mendelian disorder that affects approximately 1 in 500 to 1,000 live births. Mutations in one of two genes, PKD1 and PKD2, account for the disease in most ***ADPKD*** families. Despite the relative high frequency of PKD1 mutant alleles, compound heterozygotes or diseased homozygotes have not been described. Methods and Results: We report a family with type 1 ***ADPKD*** in which the marriage between affected first-degree cousins resulted in two live-born heterozygous offspring and two fetuses lost in late pregnancy. Genetic analysis with PKD1 and PKD2 flanking markers showed that this family is PKD1 linked (z(max) = 1.66 and -2.54 at .theta. = 0.0 for intragenic markers for PKD1 [ie, KG8] and PKD2 [ie, SPP1], respectively). Conclusion: Given a 25% chance for mutant homozygosity in the offspring of this family, our findings suggest that homozygosity of PKD1 mutations in humans is embryonically lethal, as recently documented in Pkd1 ***knockout*** mice. .COPYRGT. 2002 by the National Kidney Foundation, Inc.

L4 ANSWER 12 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
AN 2001:526306 BIOSIS
DN PREV200100526306
TI Cardiovascular, skeletal, and renal defects in mice with a targeted ***disruption*** of the Pkd1 gene.
AU Boulter, Catherine; Mulroy, Sharon; Webb, Sandra; Fleming, Stewart; Brindle, Kevin; Sandford, Richard (1)
CS (1) Addenbrooke's Hospital, Cambridge, CB2 2XY: rns13@cam.ac.uk UK
SO Proceedings of the National Academy of Sciences of the United States of America, (October 9, 2001) Vol. 98, No. 21, pp. 12174-12179. print.
ISSN: 0027-8424.
DT Article
LA English
SL English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) is characterized by cyst formation in the kidney, liver, and pancreas and is associated often with cardiovascular abnormalities such as hypertension, mitral valve prolapse, and intracranial aneurysms. It is caused by mutations in PKD1 or PKD2, encoding polycystin-1 and -2, which together form a cell surface nonselective cation ion channel. Pkd2-/- mice have cysts in the kidney and pancreas and defects in cardiac septation, whereas Pkd1del34 -/- and Pkd1L -/- mice have cysts but no cardiac abnormalities, although vascular fragility was reported in the latter. Here we describe mice carrying a targeted mutation in Pkd1 (Pkd1del17-21betageo), which defines its expression pattern by using a lacZ reporter gene and may identify novel functions for polycystin-1. Although Pkd1del17-21betageo +/- adult mice develop renal and hepatic cysts, Pkd1del17-21betageo -/- embryos die at embryonic days 13.5-14.5 from a primary cardiovascular defect that includes double outflow right ventricle, disorganized myocardium, and abnormal atrio-ventricular septation. Skeletal development is also severely compromised. These abnormalities correlate with the major sites of Pkd1 expression. During nephrogenesis, Pkd1 is expressed in maturing tubular epithelial cells from embryonic day 15.5. This expression coincides with the onset of cyst formation in Pkd1del34 -/-, Pkd1L -/-, and Pkd2-/- mice, supporting the hypothesis that polycystin-1 and polycystin-2 interact in vivo and that their failure to do so leads to abnormalities in tubule morphology and function.

L4 ANSWER 13 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7
AN 2001:492764 BIOSIS
DN PREV200100492764
TI Early development of polycystic kidney disease in ***transgenic*** mice expressing an activated mutant of the beta-catenin gene.
AU Saadi-Kheddouci, Sihem; Berrebi, Dominique; Romagnolo, Beatrice; Cluzeaud, Francoise; Peuchmaur, Michel; Kahn, Axel; Vandewalle, Alain; Perret, Christine (1)
CS (1) INSERM U129, ICGM, 24 Rue du Faubourg St Jacques, 75014, Paris: perret@icgm.cochin.inserm.fr France
SO Oncogene, (20 September, 2001) Vol. 20, No. 42, pp. 5972-5981. print.

ISSN: 0950-9232.
DT Article
LA English
SL English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) is common and is a major cause of renal failure. Although the genetics of ***ADPKD*** are well known and have led to the discovery of polycystins, a new protein family, the pathogenesis of the disease remains largely unknown. Recent studies have indicated that the beta-catenin signaling pathway is one of the targets of the transduction pathway controlled by the polycystins. We have generated ***transgenic*** mice that overproduce an oncogenic form of beta-catenin in the epithelial cells of the kidney. These mice developed severe polycystic lesions soon after birth that affected the glomeruli, proximal, distal tubules and collecting ducts. The phenotype of these mice mimicked the human ***ADPKD*** phenotype. Cyst formation was associated with an increase in cell proliferation and apoptosis. The cell proliferation and apoptotic indexes was increased 4-5-fold and 3-4-fold, respectively, in cystic tubules of the ***transgenic*** mice compared to that of littermate controls. Our findings provide experimental genetic evidence that activation of the Wnt/beta-catenin signaling pathway causes polycystic kidney disease and support the view that dysregulation of the Wnt/beta-catenin signaling is involved in its pathogenesis.

L4 ANSWER 14 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:278789 BIOSIS
DN PREV200200278789
TI Molecular defect of PKD1 gene resulting in abnormal RNA processing in a Thai family.
AU Rungroj, Nanyawan (1); Vareesangthip, Kriengsak; Wilairat, Prapon; Thongnoppakhun, Wanna (1); Sirinavin, Chintana (1); Yenchitsomanus, Pa-thai (1)
CS (1) Division of Molecular Genetics, Department of Research and Development, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, 10700 Thailand
SO Journal of the Medical Association of Thailand, (September, 2001) Vol. 84, No. 9, pp. 1308-1316. print.
ISSN: 0125-2208.
DT Article
LA English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) is a common human autosomal disorder caused mainly by mutations of the PKD1 gene. In analysis of PKD1 transcripts by long RT-PCR and nested PCR procedures, we observed PKD1-cDNA fragments from three ***ADPKD*** siblings from the same family with a size approximately 250 base pairs (bp) shorter than normal. Further investigations showed that the PKD1 transcripts from these patients had been abnormally processed, the nucleotide sequence of exon 43 containing 291 nt was missing from the transcripts, which would result in an abnormal polycystin-1 with an in-frame deletion of 97 amino acids. This splicing defect did not result from a mutation that ***disrupted*** the splice donor or acceptor sites adjacent to exon 43 or the branch sites in flanking introns but was most likely due to 20-bp deletion observed in intron 43. The intronic deletion was present in 8 affected members but absent in 11 unaffected members, corresponding with the results of genetic linkage analysis using 5 polymorphic markers in the PKD1 region. Molecular diagnosis of PKD1 in this family could, therefore, be carried out by genomic DNA amplification to directly detect the PKD1 intronic deletion.

L4 ANSWER 15 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:247477 BIOSIS
DN PREV200100247477
TI ***ADPKD*** and the catenins: Polycystin-1 binds to p120.
AU Lakkis, Montaha (1); Frischauf, Anna-Maria; Zhou, Jing
CS (1) Brigham and Women's Hospital, Harvard Medical School, 77 Ave. Louis Pasteur, Boston, MA, 02115 USA
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A892. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB Autosomal Dominant Polycystic Kidney Disease (***ADPKD***) is the leading genetic cause of renal failure, follows most commonly from defects in PKD-1 gene. The gene product of PKD-1 is an integral membrane protein with large appx2,500-aa extracellular amino terminal domain, 11 membrane spanning regions and a functional cytoplasmic carboxy terminal domain. The amino terminal domain of polycystin-1 contains multiple modules with functional candidacy, implicated in protein-protein and cell-cell interactions. Polycystin is required for normal tubulogenesis during renal development, but its precise physiologic function is not yet defined. Epithelial tubulogenesis involves complex cell rearrangement that require control of both cell adhesion and migration. Several lines of evidence suggested that additional proteins might participate in binding reactions with the amino-terminus of polycystin-1, and thereby confer signals required for normal kidney growth and development. We postulated that polycystin-1 involves in functional interactions via the amino terminus. To address this possibility, we employed the yeast two-hybrid system, using the amino terminus of polycystin-1 as a 'bait' in screening an embryonic cDNA library. We have identified a handful number of candidates, evidencing potential functional interactions between the amino terminus of polycystin-1 and proteins adducts encoded by the identified genes. Among the identified genes, one encodes a member of cadherin-associated proteins, pp120 whose function in cell-cell and cell-matrix interactions have been widely investigated. Additionally, co-immunoprecipitation studies and double-immunolabeling followed by confocal microscopy analysis, suggested that the interactions may represents a physiological complex in MDCK and 293-HEK cells, stably expressing the amino terminus of polycystin-1. We herein, provide evidence for functional interactions between polycystin-1 and p120, which helps to place polycystin-interacting protein complexes within distinct biochemical pathway. It is conceivable that the ***disruption*** of such a complex may play a role in the pathogenesis of ***ADPKD*** associated with PKD-1 mutations.

L4 ANSWER 16 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 2001:302064 BIOSIS
DN PREV200100302064
TI Tuberin-dependent membrane localization of polycystin-1: A functional link between polycystic kidney disease and the TSC2 tumor suppressor gene.
AU Kleymenova, Elena (1); Ibraghimov-Beskrovnaya, Oxana; Kugoh, Hiroyuki; Everitt, Jeff; Xu, Hui; Kiguchi, Kaoru; Landes, Greg; Harris, Peter; Walker, Cheryl (1)
CS (1) Department of Carcinogenesis, Research Division, University of Texas MD Anderson Cancer Center, Science Park, Smithville, TX, 78957: ekleymenova@mail.ciit.org, cwalker@odin.mdacc.tmc.edu USA
SO Molecular Cell, (April, 2001) Vol. 7, No. 4, pp. 823-832. print.
ISSN: 1097-2765.
DT Article
LA English
SL English
AB The PKD1 gene accounts for 85% of autosomal dominant polycystic kidney disease (***ADPKD***), the most common human genetic disorder. Rats with a germline inactivation of one allele of the Tsc2 tumor suppressor gene developed early onset severe bilateral polycystic kidney disease, with similarities to the human contiguous gene syndrome caused by germline codeletion of PKD1 and TSC2 genes. Polycystic rat renal cells retained two normal Pkd1 alleles but were null for Tsc2 and exhibited loss of lateral membrane-localized polycystin-1. In tuberin- ***deficient*** cells, intracellular trafficking of polycystin-1 was ***disrupted*** , resulting in sequestration of polycystin-1 within the Golgi and re-expression of Tsc2 restored correct polycystin-1 membrane localization. These data identify tuberin as a determinant of polycystin-1 functional localization and, potentially, ***ADPKD*** severity.

L4 ANSWER 17 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 2001:188106 BIOSIS
DN PREV200100188106
TI Role of CFTR in autosomal recessive polycystic kidney disease.
AU Nakanishi, Koichi; Sweeney, William E., Jr.; Dell, Katherine Macrae; Cotton, Calvin U.; Avner, Ellis D. (1)
CS (1) Department of Pediatrics, Rainbow Babies and Children's Hospital, 11100 Euclid Avenue, LC 6003, Cleveland, OH, 44106-6003: eda@po.cwru.edu USA
SO Journal of the American Society of Nephrology, (April, 2001) Vol. 12, No. 4, pp. 719-725. print.
ISSN: 1046-6673.
DT Article
LA English
SL English
AB An extensive body of in vitro data implicates epithelial chloride secretion, mediated through cystic fibrosis transmembrane conductance regulator (CFTR) protein, in generating or maintaining fluid filled cysts in MDCK cells and in human autosomal dominant polycystic kidney disease (***ADPKD***). In contrast, few studies have addressed the pathophysiology of fluid secretion in cyst formation and enlargement in autosomal recessive polycystic kidney disease (ARPKD). Murine models of targeted ***disruptions*** or deletions of specific genes have created opportunities to examine the role of individual gene products in normal development and/or disease pathophysiology. The creation of a murine model of CF, which lacks functional CFTR protein, provides the opportunity to determine whether CFTR activity is required for renal cyst formation in vivo. Therefore, this study sought to determine whether renal cyst formation could be prevented by genetic complementation of the BPK murine model of ARPKD with the CFTR ***knockout*** mouse. The results of this study reveal that in animals that are homozygous for the cystic gene (bpk), the lack of functional CFTR protein on the apical surface of cystic epithelium does not provide protection against cyst growth and subsequent decline in renal function. Double mutant mice (bpk -/-; cftr -/-) developed massively enlarged kidneys and died, on average, 7 d earlier than cystic, non-CF mice (bpk -/-; cftr +/+-). This suggests fundamental differences in the mechanisms of transtubular fluid secretion in animal models of ARPKD compared with ***ADPKD*** .

L4 ANSWER 18 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:299816 BIOSIS
DN PREV200200299816
TI Long term endovenous (IV) iron sucrose in anemic peritoneal dialysis (PD) patients on erythropoietin (rHEPO) treatment do not increase peritonitis

complicances: A 48 months study.
AU Scarpioni, Roberto (1); Gandolfi, Stefano; Cristinelli, Luciano (1)
CS (1) Divisione di Nefrologia e Dialisi, Piacenza AUSL Hospital, Piacenza Italy
SO Journal of the American Society of Nephrology, (September, 2001) Vol. 12, No. Program and Abstract Issue, pp. 363A. http://www.jasn.org/. print. Meeting Info.: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology San Francisco, CA, USA October 10-17, 2001
ISSN: 1046-6673.
DT Conference
LA English

L4 ANSWER 19 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 10
AN 2001:208675 BIOSIS
DN PREV200100208675
TI Polycystin-2 is a novel cation channel implicated in defective intracellular Ca2+ homeostasis in polycystic kidney disease.
AU Vassilev, Peter M. (1); Guo, Lei; Chen, Xing-Zhen; Segal, Yoav; Peng, Ji-Bin; Basora, Nuria; Babakhanlou, Hermik; Cruger, Gabrielle; Kanazirska, Marie; Ye, Chian-ping; Brown, Edward M.; Hediger, Matthias A.; Zhou, Jing (1)
CS (1) Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Room 522, Boston, MA, 02115: pvassilev@rics.bwh.harvard.edu, zhou@rics.bwh.harvard.edu USA
SO Biochemical and Biophysical Research Communications, (March 23, 2001) Vol. 282, No. 1, pp. 341-350. print.
ISSN: 0006-291X.
DT Article
LA English
SL English
AB Mutations in polycystins-1 and -2 (PC1 and PC2) cause autosomal dominant polycystic kidney disease (***ADPKD***), which is characterized by progressive development of epithelial renal cysts, ultimately leading to renal failure. The functions of these polycystins remain elusive. Here we show that PC2 is a Ca2+-permeable cation channel with properties distinct from any known intracellular channels. Its kinetic behavior is characterized by frequent transitions between closed and open states over a wide voltage range. The activity of the PC2 channel is transiently increased by elevating cytosolic Ca2+. Given the predominant endoplasmic reticulum (ER) location of PC2 and its unresponsiveness to the known modulators of mediating Ca2+ release from the ER, inositol-trisphosphate (IP3) and ryanodine, these results suggest that PC2 represents a novel type of channel with properties distinct from those of the other Ca2+-release channels. Our data also show that the PC2 channel can be translocated to the plasma membranes by defined chemical chaperones and proteasome modulators, suggesting that in vivo, it may also function in the plasma membrane under specific conditions. The sensitivity of the PC2 channel to changes of intracellular Ca2+ concentration is ***deficient*** in a mutant found in ***ADPKD*** patients. The dysfunction of such mutants may result in defective coupling of PC2 to intracellular Ca2+ homeostasis associated with the pathogenesis of ***ADPKD*** .

L4 ANSWER 20 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001421530 EMBASE
TI Characterization of microsatellite markers adjacent to AP-4 on chromosome 16p13.3.
AU Bae Y.; Kim H.; Namgoong H.; Baek M.; Lee J.; Hwang D.; Hwang Y.; Ahn C.; Kang S.
CS S. Kang, Graduate School of Biotechnology, Korea University, Seoul 136-701, Korea, Republic of. skang@korea.ac.kr
SO Molecular and Cellular Probes, (2001) 15/5 (313-315).
Refs: 5
ISSN: 0890-8508 CODEN: MCPRE6
CY United Kingdom
DT Journal; Article
FS 022 Human Genetics
LA English
SL English
AB The 1400 kb genomic sequence between the markers D16S406 and D16S423 on chromosome 16p13.3 has been recently sequenced and the interval contains a transcription factor, AP-4, that was identified as a ligand for immunoglobulin-kappa promoter E-box elements, suggesting that AP-4 may be related to immunodeficiency diseases. In addition, chromosome 16p13.3 includes a number of genes including the PKD1 gene, the autosomal dominant polycystic kidney disease (***ADPKD***) gene. ***ADPKD*** is characterized by progressive development and enlargement of renal cysts. The size and genomic complexity of the PKD1 gene makes it impractical to detect mutations for prenatal diagnosis. Therefore, pedigree-based linkage analysis remains useful for diagnosis of ***ADPKD*** . To increase the number of polymorphic markers in the region around AP-4 gene, we performed database searches of 1400 kb of genomic sequence (from contig NT000877 to NT001573: http://www.ncbi.gov/genome/seq.cgi) across the 16p13.3. A number of dinucleotide or tetranucleotide repeats were found, and 20 microsatellites that contain more than 15 contiguous repeats were chosen for further investigation. .COPYRGT. 2001 Academic Press.

L4 ANSWER 21 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 11
AN 2001403606 EMBASE
TI Development of cystic renal disease in interleukin-3 ***transgenic*** mice.
AU Ramirez Bergeron D.; Barth R.K.; Ryan C.K.
CS R.K. Barth, James P. Wilmot Cancer Center, Cancer Ctr./Dept. of Microbiology, Univ. Rochester Sch. Med./Dentistry, 601 Elmwood Ave., Rochester, NY 14642, United States
SO Transgenics, (2001) 3/2-4 (215-226).
Refs: 45
ISSN: 1023-6171 CODEN: TADTEF
CY United Kingdom
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
022 Human Genetics
028 Urology and Nephrology
029 Clinical Biochemistry
LA English
SL English
AB In an effort to discriminate the pathological effects of interleukin-3 (IL-3) in vivo, we generated IL-3 ***transgenic*** mice whose expression was driven by the cis regulatory elements of the albumin gene. In addition to liver expression of the ***transgene*** , IL-3 was also expressed in the kidneys of a number of these ***transgenic*** lines. The presence of IL-3 in the kidneys was associated with renal pathology that included the presence of cysts, glomerulosclerosis, tubular atrophy with striking myelin bodies, mesangial hypercellularity and matrix increase. Physiologic alterations included the development of azotemia, lethargy, and lethality. The pathology observed, which occurred in multiple offspring of each of six individual ***transgenic*** IL-3 lines, bears striking resemblance to autosomal dominant polycystic kidney disease (***ADPKD***) found in humans. This is the first direct model of IL-3 as a severely pathogenic molecule as these findings suggest that chronic expression of IL-3 can contribute to the development of renal disease cautioning its therapeutic utilization.

L4 ANSWER 22 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000431182 EMBASE
TI Modification of the composition of polycystin-1 multiprotein complexes by calcium and tyrosine phosphorylation.
AU Geng L.; Burrow C.R.; Li H.-P.; Wilson P.D.
CS P.D. Wilson, Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029, United States. pat.wilson@mssm.edu
SO Biochimica et Biophysica Acta - Molecular Basis of Disease, (15 Dec 2000) 1535/1 (21-35).
Refs: 71
ISSN: 0925-4439 CODEN: BBADEX
PUI S 0925-4439(00)00079-X
CY Netherlands
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
029 Clinical Biochemistry
LA English
SL English
AB Mutations in the PKD1 gene are responsible for >85% of autosomal dominant polycystic kidney disease (***ADPKD***). The protein product of PKD1, polycystin-1, is a large, modular membrane protein, with putative ligand-binding motifs in the extracellular N-terminal portion, 9-11 transmembrane domains and an intracellular C-terminal portion with phosphorylation sites. A role for polycystin-1 as a cell surface receptor involved in cell-matrix and cell-cell interactions has been proposed. In this study, we have analyzed polycystin-1 and associated protein distribution in normal human epithelial cells and examined the role of cell-matrix versus cell-cell interactions in regulation of the assembly of polycystin-1 multiprotein complexes. Immunocytochemistry, sucrose density gradient sedimentation, co-immunoprecipitation analyses and in vitro binding assays have shown that polycystin-1 associates with the focal adhesion proteins talin, vinculin, p130Cas, FAK, .alpha.-actinin, paxillin and pp60c-src in subconfluent normal human fetal collecting tubule (HFCT) epithelia when cell-matrix interactions predominate. Polycystin-1 also forms higher S value complexes with the cell-cell adherens junction proteins E-cadherin, .beta.- and .gamma.-catenins in confluent cultures when cell-cell interactions are predominant. Polycystin-1 multiprotein complexes can be ***disrupted*** by cytochalasin D but not by colchicine, suggesting involvement of the actin cytoskeleton. Although inhibition of tyrosine phosphorylation by tyrphostin inhibits polycystin-1-FAK interactions, E-cadherin interactions are enhanced. High calcium treatment also increases polycystin-1-E-cadherin interactions. (C) 2000 Elsevier Science B.V.

L4 ANSWER 23 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 12
AN 2001:198574 BIOSIS
DN PREV200100198574
TI A human PKD1 ***transgene*** generates functional polycystin-1 in mice and is associated with a cystic phenotype.
AU Pritchard, Lynn; Sloane-Stanley, Jackie A.; Sharpe, Jackie A.; Aspinwall, Richard; Lu, Weining; Buckle, Veronica; Strmecki, Lana; Walker, Denise; Ward, Christopher J.; Alpers, Charles E.; Zhou, Jing; Wood, William G.;

Harris, Peter C. (1)
CS (1) Department of Nephrology, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905: harris.peter@mayo.edu USA
SO Human Molecular Genetics, (1 November, 2000) Vol. 9, No. 18, pp. 2617-2627. print.
ISSN: 0964-6906.
DT Article
LA English
SL English
AB Three founder ***transgenic*** mice were generated with a 108 kb human genomic fragment containing the entire autosomal dominant polycystic kidney disease (***ADPKD***) gene, PKD1, plus the tuberous sclerosis gene, TSC2. Two lines were established (TPK1 and TPK3) each with apprx30 copies of the ***transgene*** . Both lines produced full-length PKD1 mRNA and polycystin-1 protein that was developmentally regulated, similar to the endogenous pattern, with expression during renal embryogenesis and neonatal life, markedly reduced at the conclusion of renal development. Tuberin expression was limited to the brain. ***Transgenic*** animals from both lines (and the TPK2 founder animal) often displayed a renal cystic phenotype, typically consisting of multiple microcysts, mainly of glomerular origin. Hepatic cysts and bile duct proliferation, characteristic of ***ADPKD*** , were also seen. All animals with two copies of the ***transgenic*** chromosome developed cysts and, in total, 48 of the 100 ***transgenic*** animals displayed a cystic phenotype. To test the functionality of the ***transgene*** , animals were bred with the Pkd1del34 ***knockout*** mouse. Both ***transgenic*** lines rescued the embryonically lethal Pkd1del34/del34 phenotype, demonstrating that human polycystin-1 can complement for loss of the endogenous protein. The rescued animals were viable into adulthood, although more than half developed hepatic cystic disease in later life, similar to the phenotype of older Pkd1del34/+ animals. The TPK mice have defined a minimal area that appropriately expresses human PKD1. Furthermore, this model indicates that over-expression of normal PKD1 can elicit a disease phenotype, suggesting that the level of polycystin-1 expression may be relevant in the human disease.

L4 ANSWER 24 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
13
AN 2000:335510 BIOSIS
DN PREV200000335510
TI Strong homophilic interactions of the Ig-like domains of polycystin-1, the protein product of an autosomal dominant polycystic kidney disease gene, PKD1.
AU Ibraghimov-Beskrovnaya, Oxana (1); Bukanov, Nikolay O.; Donohue, Lincoln C.; Dackowski, William R.; Klinger, Katherine W.; Landes, Gregory M.
CS (1) Genzyme Corporation, 1 Mountain Road, Framingham, MA, 01701-9322 USA
SO Human Molecular Genetics, (1 July, 2000) Vol. 9, No. 11, pp. 1641-1649. print.
ISSN: 0964-6906.
DT Article
LA English
SL English
AB The 14 kb mRNA of the polycystic kidney disease gene PKD1 encodes a novel
large (apprx460 kDa) protein, polycystin-1, of unknown function that is responsible for autosomal dominant polycystic kidney disease (***ADPKD***). The unique organization of multiple adhesive domains of polycystin-1, including 16 Ig-like domains (or PKD domains) suggests that it may play an important role in cell-cell/cell-matrix interactions. Here we demonstrate the localization of polycystin-1 to epithelial cell-cell contacts in culture. These results along with structural predictions prompted us to propose that polycystin-1 is involved in cell-cell adhesion through its cluster of Ig-like repeats. We show that Ig-like domains · II-XVI are involved in strong calcium-independent homophilic interactions in vitro. Domains XI-XVI form interactions with high affinity (Kd = 60 nM) and domains II-V exhibit the lowest binding affinity (Kd = 730 nM) in these studies. Most importantly, we show that antibodies raised against Ig-like domains of polycystin-1 ***disrupt*** cell-cell interactions in MDCK cell monolayers, thus indicating that polycystin-1 is directly involved in the cell-cell adhesion process. Collectively, these data suggest that interactions of the Ig-like repeats of polycystin-1 play an important role in mediating intercellular adhesion. We suggest that the loss of these interactions due to mutations in polycystin-1 may be an important step in cystogenesis.

L4 ANSWER 25 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
14
AN 2000:470965 BIOSIS
DN PREV200000470965
TI Thirteen novel mutations of the replicated region of PKD1 in an Asian population.
AU Phakdeekitcharoen, Bunyong; Watnick, Terry J.; Ahn, Curie; Whang, Dae-Yeon; Burkhart, Brian; Germino, Gregory G. (1)
CS (1) Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Ross 970, 720 Rutland Avenue, Baltimore, MD, 21205 USA
SO Kidney International, (October, 2000) Vol. 58, No. 4, pp. 1400-1412. print.
ISSN: 0085-2538.
DT Article
LA English
SL English
AB Background: Mutations of PKD1 are thought to account for approximately 85% of all mutations in autosomal dominant polycystic kidney disease (***ADPKD***). The search for PKD1 mutations has been hindered by both its large size and complicated genomic structure. To date, few mutations that affect the replicated segment of PKD1 have been described, and virtually all have been reported in Caucasian patients. Methods: In the present study, we have used a long-range polymerase chain reaction (PCR)-based strategy previously developed by our laboratory to analyze exons in the replicated region of PKD1 in a population of 41 unrelated Thai and 6 unrelated Korean families with ***ADPKD*** . We have amplified approximately 3.5 and approximately 5 kb PKD1 gene-specific fragments (5'MR and 5'LR) containing exons 13 to 15 and 15 to 21 and performed single-stand conformation analysis (SSCA) on nested PCR products. Results: Nine novel pathogenic mutations were detected, including six nonsense and three frameshift mutations. One of the deletions was shown to be a de novo mutation. Four potentially pathogenic variants, including one 3 bp insertion and three missense mutations, were also discovered. Two of the nonconservative amino acid substitutions were predicted to ***disrupt*** the three-dimensional structure of the PKD repeats. In addition, six polymorphisms, including two missense and four silent nucleotide substitutions, were identified. Approximately 25% of both the pathogenic and normal variants were found to be present in at least one of the homologous loci. Conclusion: To our knowledge, this is the first report of mutation analysis of the replicated region of PKD1 in a non-Caucasian population. The methods used in this study are widely applicable and can be used to characterize PKD1 in a number of ethnic groups using DNA samples prepared using standard techniques. Our data suggest that gene conversion may play a significant role in producing variability of the PKD1 sequence in this population. The identification of additional mutations will help guide the study of polycystin-1 and better help us to understand the pathophysiology of this common disease.

L4 ANSWER 26 OF 56 CAPLUS COPYRIGHT 2003 ACS
AN 2000:614869 CAPLUS
DN 133:294867
TI ***ADPKD*** : a human disease altering Golgi function and basolateral exocytosis in renal epithelia
AU Charron, Audra J.; Bacallao, Robert L.; Wandinger-Ness, Angela
CS Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, NM, USA
SO Traffic (Copenhagen) (2000), 1(8), 675-686
CODEN: TRAFFA; ISSN: 1398-9219
PB Munksgaard International Publishers Ltd.
DT Journal
LA English
AB Epithelial cells explanted from autosomal dominant polycystic kidney disease (***ADPKD***) tissue exhibit impaired exocytosis, specifically between the Golgi and basolateral membrane. Here the defect is shown to result in the accumulation of the basolateral transport marker vesicular stomatitis virus (VSV) G protein in the Golgi complex. Golgi complex morphol. is consequently altered in the disease cells, evident in the noticeable fenestration and dilation of the cisternae. Further detailed microscopic evaluation of normal kidney and ***ADPKD*** cells revealed that ineffective basolateral exocytosis correlated with modulations in the localization of select post-Golgi transport effectors. The cytosolic coat proteins p200/myosin II and caveolin exhibited enhanced assocn. with the cytoskeleton or the Golgi of the disease cells, resp. Most cytoskeletal components with known roles in vesicle translocation or formation were normally arrayed with the exception of Golgi .beta.-spectrin, which was less prevalent on vesicles. The rab8 GTPase, important for basolateral vesicle targeting, was redistributed from the perinuclear Golgi region to disperse vesicles in ***ADPKD*** cells. At the basolateral membrane of ***ADPKD*** cells, there was a notable loss of the exocyst components sec6/s8 and an unidentified syntaxin. It is postulated that dysregulated basolateral transport effector function ppts. the ***disruption*** of basolateral exocytosis and dilation of the ***ADPKD*** cell Golgi as basolateral cargo accumulates within the cisternae.
RE.CNT 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:252484 BIOSIS
DN PREV200200252484
TI Tubular microcysts in HIV-associated nephropathy (HIVAN) are similar to cysts in autosomal dominant polycystic kidney disease (***ADPKD*** .
AU Ross, Michael J. (1); Bruggeman, Leslie A. (1); Wilson, Patricia D. (1); Klotman, Paul E. (1)
CS (1) Div. of Nephrology, Mt. Sinai Sch. of Med., New York, NY USA
SO Journal of the American Society of Nephrology, (September, 2000) Vol. 11, No. Program and Abstract Issue, pp. 550A. http://www.jasn.org/. print.
Meeting Info.: 33rd Annual Meeting of the American Society of Nephrology and the 2000 Renal Week Toronto, Ontario, Canada October 10-16, 2000
ISSN: 1046-6673.
DT Conference
LA English

L4 ANSWER 28 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

15
AN 2000:190714 BIOSIS
DN PREV200000190714
TI Genetic evidence for a trans-heterozygous model for cystogenesis in autosomal dominant polycystic kidney disease.
AU Koptides, Michael; Mean, Richard; Demetriou, Kyproula; Pierides, Alkis; Deltas, C. Constantinou (1)
CS (1) Department of Molecular Genetics, Cyprus Institute of Neurology and Genetics, 6 International Airport Avenue, Ayios Dhometios, 1683, Nicosia Cyprus
SO Human Molecular Genetics, (Feb. 12, 2000) Vol. 9, No. 3, pp. 447-452. ISSN: 0964-6906.
DT Article
LA English
SL English
AB Polycystic kidney disease (***ADPKD***) is a condition with an autosomal dominant mode of inheritance and adult onset. Two forms of the disease, ADPKD1 and ADPKD2, caused by mutations in PKD1 and PKD2, respectively, are very similar, except that ADPKD1 patients run a more severe course. At the cellular level, ADPKD1 was first shown to be recessive, since somatic second hits are perhaps necessary for cyst formation. The near identical phenotype had suggested that ADPKD1 and ADPKD2 might have a similar pathogenesis and that the two gene products, polycystins 1 and 2, are part of a common developmental pathway. Work in ***transgenic*** mice showed that somatic loss of Pkd2 expression is necessary for renal cyst formation, and recently we showed that somatic mutations inactivating the inherited healthy allele were present in 9 of 23 cysts from a human ADPKD2 kidney, supporting a two-hit loss-of-function model for ADPKD2 cystogenesis. Here, we provide the first direct genetic evidence that polycystins 1 and 2 do interact, perhaps as part of a larger complex. In cystic DNA from a kidney of an ADPKD1 patient, we showed somatic mutations not only in the PKD1 gene of certain cysts, but also in the PKD2 gene of others, generating a trans-heterozygous state with mutations in both genes. One mutation in PKD1 is of germinal nature and the mutation in the PKD2 gene is of somatic nature. The implications of such a situation are enormous, not only for ***ADPKD*** , but also for many other conditions with phenotypic heterogeneity and age-dependent penetrance.

L4 ANSWER 29 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
16
AN 2000:228062 BIOSIS
DN PREV200000228062
TI Compromised cytoarchitecture and polarized trafficking in autosomal dominant polycystic kidney disease cells.
AU Charron, Audra J.; Nakamura, Sakie; Bacallao, Robert; Wandinger-Ness, Angela (1)
CS (1) Department of Pathology, University of New Mexico Health Sciences Center, 2325 Camino de Salud CRF 225, Albuquerque, NM, 87131-5301 USA
SO Journal of Cell Biology, (April 3, 2000) Vol. 149, No. 1, pp. 111-124. ISSN: 0021-9525.
DT Article
LA English
SL English
AB Cystogenesis associated with autosomal dominant polycystic kidney disease (***ADPKD***) is characterized by perturbations in the polarized phenotype and function of cyst-lining epithelial cells. The polycystins, the protein products of the genes mutated in the majority of ***ADPKD*** cases, have been described recently, but the pathological mechanism by which causal mutations result in the mislocalization of cell membrane proteins has remained unclear. This report documents the dissociation from the ***ADPKD*** cell basolateral membrane of three molecules essential for spatial organization and exocytosis. The adherens junction protein E-cadherin, the subcellular disposition of which governs intercellular and intracellular architecture, was discovered sequestered in an internal ***ADPKD*** cell compartment. At the same time, sec6 and sec8, components of a complex critical for basolateral cargo delivery normally arrayed at the apico-lateral apex, were depleted from the ***ADPKD*** cell plasma membrane. An analysis of membrane transport revealed that basolateral trafficking of proteins and lipids was impaired as a result of delayed cargo exit from the ***ADPKD*** cell Golgi apparatus. Apical transport proceeded normally. Taken together with recent documentation of an association between polycystin-1 and E-cadherin (Huan and van Adelsberg, 1999), the data suggest that causal mutations ***disrupt*** E-cadherin-dependent cytoarchitecture, adversely affecting protein assemblies crucial for basolateral trafficking.

L4 ANSWER 30 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
17
AN 2000:191990 BIOSIS
DN PREV200000191990
TI Cardiac defects and renal failure in mice with targeted mutations in Pkd2.
AU Wu, Guanqing; Markowitz, Glen S.; Li, Li; D'Agati, Vivette D.; Factor, Stephen M.; Geng, Lin; Tibara, Sonia; Tuchman, Jay; Cai, Yiqiang; Park, Jong Hoon; van Adelsberg, Janet; Hou, Harry, Jr.; Kucherlapati, Raju; Edelmann, Winfried; Somlo, Stefan (1)
CS (1) Section of Nephrology, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT USA
SO Nature Genetics, (Jan., 2000) Vol. 24, No. 1, pp. 75-78. ISSN: 1061-4036.
DT Article
LA English
SL English
AB PKD2, mutations in which cause autosomal dominant polycystic kidney disease (***ADPKD***), encodes an integral membrane glyco-protein with similarity to calcium channel subunits. We induced two mutations in the mouse homologue Pkd2 (ref. 4): an unstable allele (WS25; hereafter denoted Pkd2WS25) that can undergo homologous-recombination-based somatic rearrangement to form a null allele; and a true null mutation (WS183; hereafter denoted Pkd2-). We examined these mutations to understand the function of polycystin-2, the protein product of Pkd2, and to provide evidence that kidney and liver cyst formation associated with Pkd2 ***deficiency*** occurs by a two-hit mechanism. Pkd2-/- mice die in utero between embryonic day (E) 13.5 and parturition. They have structural defects in cardiac septation and cyst formation in maturing nephrons and pancreatic ducts. Pancreatic ductal cysts also occur in adult Pkd2WS25/- mice, suggesting that this clinical manifestation of ***ADPKD*** also occurs by a two-hit mechanism. As in human ***ADPKD*** , formation of kidney cysts in adult Pkd2WS25/- mice is associated with renal failure and early death (median survival, 65 weeks versus 94 weeks for controls). Adult Pkd2+/- mice have intermediate survival in the absence of cystic disease or renal failure, providing the first indication of a deleterious effect of haploinsufficiency at Pkd2 on long-term survival. Our studies advance our understanding of the function of polycystin-2 in development and our mouse models recapitulate the complex human ***ADPKD*** phenotype.

L4 ANSWER 31 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
18
AN 2001:71899 BIOSIS
DN PREV200100071899
TI Modification of the composition of polycystin-1 multiprotein complexes by calcium and tyrosine phosphorylation.
AU Geng, Lin; Burrow, Christopher R.; Li, Hsi-Ping; Wilson, Patricia D. (1)
CS (1) Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY, 10029: pat.wilson@.mssm.edu USA
SO Biochimica et Biophysica Acta, (15 December, 2000) Vol. 1535, No. 1, pp. 21-35. print. ISSN: 0006-3002.
DT Article
LA English
SL English
AB Mutations in the PKD1 gene are responsible for > 85% of autosomal dominant polycystic kidney disease (***ADPKD***). The protein product of PKD1, polycystin-1, is a large, modular membrane protein, with putative ligand-binding motifs in the extracellular N-terminal portion, 9-11 transmembrane domains and an intracellular C-terminal portion with phosphorylation sites. A role for polycystin-1 as a cell surface receptor involved in cell-cell interactions has been proposed. In this study, we have analyzed polycystin-1 and associated protein distribution in normal human epithelial cells and examined the role of cell-matrix versus cell-cell interactions in regulation of the assembly of polycystin-1 multiprotein complexes. Immunocytochemistry, sucrose density gradient sedimentation, co-immunoprecipitation analyses and in vitro binding assays have shown that polycystin-1 associates with the focal adhesion proteins talin, vinculin, p130Cas, FAK, alpha-actinin, paxillin and pp60c-src in subconfluent normal human fetal collecting tubule (HFCT) epithelia when cell-matrix interactions predominate. Polycystin-1 also forms higher S value complexes with the cell-cell adherens junction proteins E-cadherin, beta- and gamma-catenins in confluent cultures when cell-cell interactions are predominant. Polycystin-1 multiprotein complexes can be ***disrupted*** by cytochalasin D but not by colchicine, suggesting involvement of the actin cytoskeleton. Although inhibition of tyrosine phosphorylation by tyrphostin inhibits polycystin-1-FAK interactions, E-cadherin interactions are enhanced. High calcium treatment also increases polycystin-1-E-cadherin interactions.

L4 ANSWER 32 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001134072 EMBASE
TI Laboratory diagnosis of inherited disorders and congenital anomalies in Bulgaria.
AU Kremensky I.; Jordanova A.; Michaylova E.; Todorova A.; Ivanova M.; Petkova R.; Andonova S.; Savov A.; Zaharova B.; Iankova S.; Kaneva R.; Kalaydjieva L.
CS Prof. I. Kremensky, Laboratory of Molecular Pathology, Univ. Hosp. of Obstet. and Gynecol., 2 Zdrave Str., Sofia 1431, Bulgaria. kremensk@medfac.acad.bg
SO Balkan Journal of Medical Genetics, (2000) 3/4 (13-21). Refs: 18
ISSN: 1311-0160 CODEN: BJMGFN
CY Macedonia
DT Journal; Article
FS 022 Human Genetics
029 Clinical Biochemistry
036 Health Policy, Economics and Management
LA English
SL English
AB Laboratory of Molecular Pathology in Sofia, Bulgaria is a national centre for diagnosis and prophylaxis of inherited metabolic diseases. The laboratory performs: 1) Mass neonatal screening for PKU (up to now 1 500 000 new-borns were screened, 56 patients with classical PKU were detected); 2) Selective biochemical screening for over 70 inborn disorders

of metabolism (up to now 66 of 472 patients were precisely diagnosed); 3) Prenatal metabolic and enzymatic diagnosis (up to now 89 prenatal diagnoses for 15 different disorders were performed); 4) Prenatal second and first trimester biochemical screening for Down syndrome (DS) and neural tube defects (NTD). Second trimester DS serum screening of 1604 preselected patients (24% of them above age of 35) detected 10 of 13 Down syndrome fetuses (seven of them in patients above age of 35 and 3 in younger women). Sonographic markers diagnosed a foetus, missed by the serum screening. DNA analysis for DS (using 3 highly informative polymorphic markers of the STR type) proved to be 15 times faster and 6 times cheaper compared to the conventional techniques; 5) DNA diagnosis for 12 most common monogenic disorders (CF, PKU, SMA, DMD/BMD, LGMD2C,
CMT, HMSNL, Haemophilia A, .beta. - thalassemia, Wilson's disease, ***ADPKD*** type 1 and 2 and galactokinase ***deficiency*** - in 922 families; 6) Prenatal diagnosis for CF, SMA, DMD/BMD, PKU, Haemophilia A, .beta. - thalassemia - in 241 families. Conclusion: For small countries with limited resources the centralised model of genetic cervices offers a series of advantages. The same infrastructure, communications and genetic register are used for the different screening programs with the same analytical techniques for most of the cases.

L4 ANSWER 33 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000066333 EMBASE
TI Molecular genetics and mechanism of autosomal dominant polycystic kidney disease.
AU Wu G.; Somlo S.
CS G. Wu, Section of Nephrology, Department of Internal Medicine, Yale University School of Medicine, P.O. Box 208029, New Haven, CT 06520-8029, United States. guanqing.wu@yale.edu
SO Molecular Genetics and Metabolism, (2000) 69/1 (1-15).
Refs: 94
ISSN: 1096-7192 CODEN: MGMEFF
CY United States
DT Journal; (Short Survey)
FS 005 General Pathology and Pathological Anatomy
022 Human Genetics
LA English
SL English
AB Considerable progress toward understanding pathogenesis of autosomal dominant polycystic disease (***ADPKD***) has been made during the past 15 years. ***ADPKD*** is a heterogeneous human disease resulting from mutations in either of two genes, PKD1 and PKD2. The similarity in the clinical presentation and evidence of direct interaction between the COOH termini of polycystin-1 and polycystin-2, the respective gene products, suggest that both proteins act in the same molecular pathway. The fact that most mutations from ***ADPKD*** patients result in truncated polycystins as well as evidence of a loss of heterozygosity mechanism in individual PKD cysts indicate that the loss of the function of either PKD1 or PKD2 is the most likely pathogenic mechanism for ***ADPKD*** . A novel mouse model, WS25, has been generated with a targeted mutation at Pkd2 locus in which a mutant exon 1 created by inserting a neo(r) cassette exists in tandem with the wild-type exon 1. This causes an unstable allele that undergoes secondary recombination to produce a true null allele at Pkd2 locus. Therefore, the model Pkd2(WS25/-), which carries the WS25 unstable allele and a true null allele, produces somatic second hits during mouse development or adult life and establishes an extremely faithful model of human ***ADPKD*** . (C) 2000 Academic Press.

L4 ANSWER 34 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
19
AN 1999:509733 BIOSIS
DN PREV199900509733
TI Autosomal dominant polycystic kidney disease: Clues to pathogenesis.
AU Harris, Peter C. (1)
CS (1) MRC Molecular Haematology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, OX3 9DS UK
SO Human Molecular Genetics, (1999) Vol. 8, No. 10, pp. 1861-1866.
ISSN: 0964-6906.
DT General Review
LA English
SL English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) is caused by mutation of one of two genes: PKD1 (16p13.3) or PKD2 (4q13-23). PKD1 accounts for apprx85% of pedigrees and is associated with significantly more severe cystic disease. The ***ADPKD*** genes encode proteins, polycystin-1 and polycystin-2, which are very different in size and structure, but which have a region of homology and may interact as part of the same complex. Polycystin-1 is a large, integral membrane protein (apprx460 kDa) predicted to be involved in cell-cell and/or cell-matrix interactions. Polycystin-2 (apprx110 kDa) is related to polycystin-1 and voltage-activated and transient receptor potential channel subunits, suggesting that the polycystins may also be associated with ion transport. A polycystin complex could regulate cellular events (that are abnormal in ***ADPKD***) in response to specific extracellular cues, mediated by controlling cellular Ca2+ levels and/or other signalling pathways. Recently, two further polycystin-like molecules have been identified, indicating roles for this novel protein family beyond the kidney. A wide range of different mutations to the PKD1 or PKD2 gene have been detected, most predicted to truncate and inactivate the proteins. A somatic second hit may be required for focal cyst development, although there is widespread immunohistochemical evidence of polycystin expression in cystic epithelia. ***Disruption*** of the mouse Pkd1 gene leads to death in the perinatal period with massive cystic expansion in homozygotes and age-related cyst development in heterozygotes. Normal renal development in Pkd1del34/del34 mice up to embryonic day apprx15.5 suggests a role for polycystin-1 in developing and maintaining the tubular architecture, consistent with the localization of the protein, rather than nephron induction. Renal cystic disease in homo- and heterozygotes of a Pkd2 mouse model with a ***disrupted*** exon 1 inserted in tandem with the normal exon (and prone to somatic recombination, which inactivates the gene) supports a role for somatic events in cystogenesis.

L4 ANSWER 35 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999082075 EMBASE
TI Cyst formation in ***ADPKD*** : New insights from natural and targeted mutants.
AU Ong A.C.M.
CS A.C.M. Ong, Institute of Molecular Medicine, University of Oxford, Oxford OX3 9DS, United Kingdom
SO Nephrology Dialysis Transplantation, (1999) 14/3 (544-546).
Refs: 20
ISSN: 0931-0509 CODEN: NDTREA
CY United Kingdom
DT Journal; Editorial
FS 022 Human Genetics
028 Urology and Nephrology
LA English

L4 ANSWER 36 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
20
AN 1999:266596 BIOSIS
DN PREV199900266596
TI Cystic diseases of the kidney: Role of adhesion molecules in normal and abnormal tubulogenesis.
AU Wilson, Patricia D. (1); Burrow, Christopher R.
CS (1) Department of Medicine/Division of Nephrology, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY, 10029 USA
SO Experimental Nephrology, (March-April, 1999) Vol. 7, No. 2, pp. 114-124.
ISSN: 1018-7782.
DT General Review
LA English
SL English
AB This short review summarizes some information concerning what is known about matrix adhesion molecules, focal adhesion proteins, and cell-cell adhesion molecules in normal renal development and cystic diseases of the kidney. The focus is on human nephrogenesis and disease, but utilizes critical information gained from genetically manipulated mouse models. Interestingly, a significant role for the human PKD-1-encoded gene product, polycystin-1, has been found in cell-matrix interactions via integrins during development, and mutations lead to autosomal dominant polycystic kidney disease (***ADPKD***). Recent studies on human ***ADPKD*** have implicated polycystin-1 in the formation of multiprotein complexes containing focal adhesion proteins at the basal cell surface of the normal ureteric bud. Further evidence of a critical role of cell-matrix interactions via focal adhesion complex formation is provided by the development of renal cystic disease in tensin ***knockout*** mice.

L4 ANSWER 37 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
21
AN 1998:326685 BIOSIS
DN PREV199800326685
TI Increased epithelial cell proliferation and abnormal extracellular matrix in rat polycystic kidney disease.
AU Ramasubbu, Kumudha; Gretz, Norbert; Bachmann, Sebastian (1)
CS (1) AG Anatomie Charite, Haus 31, Spandauer Damm 130, D-14050 Berlin Germany
SO Journal of the American Society of Nephrology, (June, 1998) Vol. 9, No. 6, pp. 937-945.
ISSN: 1046-6673.
DT Article
LA English
AB Proliferation of renal tubular epithelial cells is considered a major factor leading to cyst formation in human polycystic kidney disease (PKD). The Han:SPRD rat model for inherited PKD permits a close scrutiny, especially for early stages of the disease, and shows numerous similarities to human autosomal dominant PKD (***ADPKD***). In this study, the exact in vivo proliferation rate in Han:SPRD rat kidneys was evaluated in a cell type-specific manner, using immunohistochemistry with antibody to proliferating cell nuclear antigen (PCNA). The proliferation index (PI; percentage of PCNA-positive cell nuclei) was determined in normal and cystically altered tissue, and a relationship between proliferative activity and alterations in extracellular matrix expression was established using in situ hybridization for collagen I and IV mRNA. Heterozygously affected rats (cy/+) showed strong increases of PI values in cystically altered nephron portions that were mostly derived from proximal tubule. Cell proliferation obviously preceded cyst formation, because early in the progression of the disease, the normal-appearing tubules from PKD kidneys had markedly increased PI values compared with healthy controls (14.1-fold in 3-mo-old rats and 11.9-fold in 12-mo-old rats; $P < 0.05$), whereas later stages revealed a more generalized cystic

degeneration of the nephron, with increases in PI between 14- and 82-fold, depending on the respective category of cystic epithelia. In cysts with a distal phenotype, changes were less pronounced. No significant differences were encountered between the two age groups. Proliferation was also present in interstitial cells, whereas glomeruli were unchanged. Increases in epithelial and interstitial proliferation coincided with an overexpression of matrix compounds. For comparison, changes in homozygously affected rats (cy/cy) showed up to several hundred-fold elevated PI values. These results indicate that in the Han: SPRD model for ***ADPKD*** , cystic malformation of the nephron is preceded by and coincides with enhanced epithelial and interstitial cell proliferation. Altered cell-matrix interactions seem to be directly involved in the ***disruption*** of epithelial differentiation.

L4 ANSWER 38 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
22
AN 1998:101450 BIOSIS
DN PREV199800101450
TI Polycystic kidney disease in SBM ***transgenic*** mice: Role of c-myc in disease induction and progression.
AU Trudel, M. (1); Barisoni, L.; Lanoix, J.; D'Agati, V.
CS (1) Inst. Recherches Clin. Montreal, 110 Avenue des Pins ouest, Montreal, PQ H2W 1R7 Canada
SO American Journal of Pathology, (Jan., 1998) Vol. 152, No. 1, pp. 219-229. ISSN: 0002-9440.
DT Article
LA English
AB SBM mouse is a unique ***transgenic*** model of polycystic kidney disease (PKD) produced by dysregulation of c-myc in the kidneys. Our previous demonstration that c-myc is overexpressed in human ***autosomal*** ***polycystic*** ***kidney*** ***disease*** (***ADPKD***) prompted us to investigate the pathogenetic role of c-myc in the induction and progression of the cystogenic phenotype in our mouse model. In young SBM kidneys, c-myc was two- to threefold increased with persistent expression levels into adulthood, an age when c-myc is normally undetectable. in situ hybridization analysis of the c-myc ***transgene*** demonstrated intense signal specifically overlying glomerular and tubular epithelium of developing cysts in fetal and young kidneys. Increased expression of c-myc correlated with the Initiation and progression of the PKD phenotype as evidenced by early tubular and glomerular cysts at E16-5. Cyst number and size increased with age, with co-development of glomerular and tubular epithelial hyperplasia. Consistently, the mean renal proliferative index was increased apprx5- to 20-fold in noncystic and cystic tubules of newborn SBM animals compared with littermate controls. Similarly, in fetal and newborn kidneys the tubular apoptotic indices were increased apprxthree- to nine-fold over controls. Both proliferation and apoptotic rates in cystic tubules approached levels in developing tubules from the normal nephrogenic zone. We conclude that the pathogenesis of PKD hinges on a critical imbalance in c-myc regulation of the opposing processes of cell proliferation and apoptosis, recapitulating the cellular phenomena in developing fetal kidney.

L4 ANSWER 39 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
23
AN 1998:312561 BIOSIS
DN PREV199800312561
TI Renal tubular dysfunction in patients with cystic disease of the kidneys.
AU Pabico, Rufino C. (1); McKenna, Barbara A.; Freeman, Richard B.
CS (1) Nephrol. Unit, Dep. Med., Univ. Rochester Med. Cent., 601 Elmwood Ave., Rochester, NY 14642 USA
SO Urology, (May, 1998) Vol. 51, No. 5A SUPPL., pp. 156-160. ISSN: 0090-4295.
DT Article
LA English
AB Objective. To define the renal tubular functional abnormalities in patients with cystic disease of the kidneys. Methods. Patients with autosomal dominant polycystic kidney disease (***ADPKD***) (n = 4) and medullary sponge kidneys (MSK) (n = 3) with normal glomerular filtration rate (GFR), determined by inulin clearance, and effective renal plasma flow (ERPF), measured by p-aminohippurate clearance, underwent measurement of proximal and distal tubular functions. Proximal tubular functions were determined by the maximum reabsorption of glucose (TMGlucose) and the maximum secretion of p-aminohippurate (TmPAH). Distal tubular functions were measured by the maximum urinary concentrating and diluting mechanisms, and the urinary acidification response to acid load. Results. TMGlucose was low in both groups (209 +- 25 mg/min/1.73 in the ***ADPKD*** group and 110 +- 28 mg/min/1.73 m2 in the MSK, compared with 375 +- 40 mg/min/1.73 m2 in healthy controls; P < 0.05). Likewise, TmPAH was significantly diminished in patients with ***ADPKD*** (72 +- 6 mg/min/1.73 m2) and MSK (63 +- 5 mg/min/1.73 m2) when compared with healthy controls (89 +- 4 mg/min/1.73 m2; p < 0.05). Urinary maximum concentration after fluid deprivation was impaired in both ***ADPKD*** and MSK patients, but the diluting mechanism was intact. Finally, the ability to excrete urinary ammonium and titratable acids following an oral acid load was inadequate in both the ***ADPKD*** and MSK groups. Conclusions. Proximal and distal tubular functions are impaired in patients with ***ADPKD*** and MSK when GFR and ERPF are normal, indicating tubular ***disruption*** by the cysts and the alteration of the tubulointerstitial vascular relationship.

L4 ANSWER 40 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
24
AN 1997:219893 BIOSIS
DN PREV199799526397
TI Vascular expression of polycystin.
AU Griffin, Matthew D.; Torres, Vincente E. (1); Grande, Joseph P.; Kumar, Rajiv
CS (1) Div. Nephrology Internal Med., Mayo Clinic, 200 Second St. SW, Rochester, MN 55905 USA
SO Journal of the American Society of Nephrology, (1997) Vol. 8, No. 4, pp. 616-626. ISSN: 1046-6673.
DT Article
LA English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) is predominantly caused by mutations of the gene PKD1, which encodes a large protein, polycystin, of unknown function. A variety of arterial abnormalities occur with increased prevalence in ***ADPKD*** patients. Using an antiserum against the nonduplicated region of the polycystin protein, immunostaining of vascular smooth muscle cells was detected in normal adult elastic arteries. Partial digestion of tissue slices with nonspecific proteases greatly enhanced this staining. Similar enhancement was seen with specific elastase digestion. Immunostaining for smooth muscle actin was not affected by elastase. Antiserum preadsorbed with peptide antigen gave no staining. In specimens of intracranial aneurysms, aortic dissections, and dolichoectatic arteries from thirteen patients with ***ADPKD*** , immunostaining of variable intensity for polycystin was demonstrated in arterial smooth muscle cells and myofibroblasts, along with ***disruption*** of elastic laminae. Further elastase digestion did not significantly alter staining patterns. Intracranial aneurysms from patients without ***ADPKD*** also showed a variable degree of immunostaining with polycystin antisera in the same distribution. The expression of polycystin in arterial smooth muscle suggests a direct pathogenic role for ***ADPKD*** -related mutations in the arterial complications of this disease.

L4 ANSWER 41 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
25
AN 1997:212285 BIOSIS
DN PREV199799511488
TI Expression and localization of the water channels in human autosomal dominant polycystic kidney disease.
AU Hayashi, Matsuhiko (1); Yamaji, Yasuyoshi; Monkawa, Toshiaki; Yoshida, Tadashi; Tsuganezawa, Hirohiko; Sasamura, Hiroyuki; Kitajima, Waichi; Sasaki, Sei; Ishibashi, Kennichi; Maumo, Fumiaki; Saruta, Takao
CS (1) Dep. Internal Med., Sch. Med., Keio Univ., 35 Shinanomachi, Shinjuku-ku, Tokyo 160 Japan
SO Nephron, (1997) Vol. 75, No. 3, pp. 321-326. ISSN: 0028-2766.
DT Article
LA English
AB To characterize the cyst-lining cells in human autosomal dominant polycystic kidney disease (***ADPKD***), we performed immunohistological studies with specific antibodies against human aquaporin-2 (AQP-2, the vasopressin-regulated water channel) and aquaporin-3 (AQP-3), which are expressed only in collecting duct cells in the normal kidney. The polycystic kidney samples were obtained from 2 hemodialysis patient at uninephrectomy. Immunohistochemical studies revealed two types of staining of cyst-lining cells. Approximately 30% of all the cysts were simultaneously immunostained by both antibodies. Among these AQP-positive cysts, more than 90% of the cysts were intensely stained, with well-polarized localization of AQP-2 and AQP-3. In fewer than 10% of AQP-positive cysts, by contrast, immunostaining for AQP-2 and AQP3 was faint and no clearly polarized localization of the channels was observed. We examined the immunostaining in further detail by electron microscopy. Staining specific for AQP-2 was mainly observed in the apical membrane of cyst-lining cells. Moreover, staining specific for AQP-3 was observed in all of the AQP-2-positive cysts. It appeared unlikely that the variations in immunostaining observed under the light microscope had been induced by total ***disruption*** of water-channel polarity. The present study suggests that about 30% of the cysts in our cases of ***ADPKD*** were derived from the collecting duct cells and that the cyst-lining cells were well differentiated in terms of AQP expression.

L4 ANSWER 42 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
26
AN 1997:303987 BIOSIS
DN PREV199799603170
TI PKD1 interacts with PKD2 through a probable coiled-coil domain.
AU Qian, Feng; Germino, F. Joseph; Cai, Yiqiang; Zhang, Xiangbin; Somlo, Stefan; Germino, Gregory G. (1)
CS (1) Dep. Med., Div. Nephrol./Ross 970, Johns Hopkins Univ. Sch. Med., Baltimore, MD 21205 USA
SO Nature Genetics, (1997) Vol. 16, No. 2, pp. 179-183. ISSN: 1061-4036.
DT Article
LA English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) describes a

group of at least three genetically distinct disorders with almost identical clinical features that collectively affects 1:1,000 of the population. Affected individuals typically develop large cystic kidneys and approximately one half develop end-stage renal disease by their seventh decade. It has been suggested that the diseases result from defects in interactive factors involved in a common pathway. The recent discovery of the genes for the two most common forms of ***ADPKD*** has provided an opportunity to test this hypothesis. We describe a previously unrecognized coiled-coil domain within the C terminus of the PKD1 gene product, polycystin, and demonstrate that it binds specifically to the C terminus of PKD2. Homotypic interactions involving the C terminus of each are also demonstrated. We show that naturally occurring pathogenic mutations of PKD1 and PKD2 ***disrupt*** their associations. We have characterized the structural basis of their heterotypic interactions by deletional and site-specific mutagenesis. Our data suggest that PKD1 and PKD2 associate physically in vivo and may be partners of a common signalling cascade involved in tubular morphogenesis.

L4 ANSWER 43 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
27
AN 1997:118294 BIOSIS
DN PREV199799417497
TI Dominantly transmitted glomerulocystic kidney disease: A distinct genetic entity.
AU Sharp, Cindy K.; Bergman, Suzanne M.; Stockwin, John M.; Robbin, Michelle L.; Galliani, Carlos; Guay-Woodford, Lisa M. (1)
CS (1) Div. Nephorol., Univ. Alabama Birmingham, 624 Zeigler Res. Building, 703 South 19th St., Birmingham, AL 35294 USA
SO Journal of the American Society of Nephrology, (1997) Vol. 8, No. 1, pp. 77-84.
ISSN: 1046-6673.
DT Article; (CASE STUDY)
LA English
AB Glomerulocystic kidney disease (GCKD) is a relatively rare condition with both a sporadic and familial occurrence. Pathologically, GCKD is characterized by cystic dilatation of Bowman's space and the initial proximal convoluted tubule. As a heritable disorder, GCKD has primarily been recognized in infants with a family history of classic, autosomal dominant polycystic kidney disease (***ADPKD***). Dominantly transmitted GCKD associated with either hypoplastic or normal-sized kidneys has also been reported in older children and adults. A large, three-generation African-American family with familial GCKD is characterized. Of the 20 individuals available for study, seven affected individuals were identified by renal sonogram or renal histopathology. GCKD in this family segregates as an autosomal dominant trait as evidenced by its apparent transmission from a father to his sons. A set of directed linkage strategies indicates that the distinctive GCKD phenotype in this family results from a dominantly acting mutation that ***disrupts*** a genetic locus distinct from the ***ADPKD*** loci, PKD1 and PKD2, as well the human homologue of mouse jcpk mutation, a newly described murine GCKD. These analyses are the first known genetic studies conducted in a family with heritable GCKD and postinfantile age of onset.

L4 ANSWER 44 OF 56 CAPLUS COPYRIGHT 2003 ACS
AN 1998:97865 CAPLUS
DN 128:216149
TI The TSC2/PKD1 contiguous gene syndrome
AU Harris, Peter C.
CS MRC Molecular Haematology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK
SO Contributions to Nephrology (1997), 122(Hereditary Kidney Diseases), 76-82
CODEN: CNEPDD; ISSN: 0302-5144
PB S. Karger AG
DT Journal
LA English
AB Tuberous sclerosis (TSC) is a dominantly inherited, multi-system disorder characterized by the development of benign tumors (hamartoma), particularly in the brain, skin and kidney. TSC is genetically heterogeneous with loci in the chromosome regions 9q34 (TSC1) and 16p13.3 (TSC2). The TSC2 has been cloned and found to be next to the major autosomal dominant polycystic kidney disease (***ADPKD***) locus (PKD1). Previous studies have suggested a role of the PKD1 gene in severe, early onset cases of PKD with TSC. Here we show that in 18 TSC cases diagnosed in infancy with enlarged and polycystic kidneys, all had deletions ***disrupting*** the coding region of the PKD1 gene, as well as the TSC2 gene. We found that of the 17 cases to have germline deletions involving both genes, a consistent pattern emerged of disease manifesting at an early age and a poor renal prognosis. One surprising finding was the level of mosaicism, 7 of 25 contiguous deletions were due to somatic mutations. Involvement of the PKD1 gene is implicated in most cases of renal cystic disease in TSC through deletion (somatic or germline) and possibly through other mutations which influence expression.

L4 ANSWER 45 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
28
AN 1997:180181 BIOSIS
DN PREV199799471894
TI Autosomal dominant polycystic kidney disease.
AU Pirson, Yves (1); Chauveau, Dominique; Watson, Michael L.; Zeier, Martin; Breuning, Martin H.
CS (1) Clin. Univ. Saint-Luc, Univ. Cathol. Louvain, 10 avenue Hippocrate, 1200 Bruxelles Belgium
SO M-S (Medecine Sciences), (1997) Vol. 13, No. 1, pp. 37-44.
ISSN: 0767-0974.
DT General Review
LA French
SL French; English
AB Autosomal dominant polycystic kidney disease (***ADPKD***), the most frequent inherited kidney disease, usually manifest in adulthood, is characterized by the development of multiple renal cysts variably associated with extra-renal abnormalities. Pathophysiologic studies have shown that expansion of kidney cysts results from transepithelial fluid secretion and cellular proliferation of relatively immature cells, in association with remodeling of the tubular basement membrane. Interstitial fibrosis and widespread apoptosis likely contribute to the loss of renal function. Clinical determinants of progression to renal insufficiency are the genetic form of the disease, gender and probably blood pressure level. Liver cysts, occurring in 80% of patients by age 50, are usually asymptomatic. Some patients with massive polycystic liver may require cyst fenestration and/or resection. Cerebral aneurysm is detected in 8% of patients overall, and in 16% of those with a family history of cerebral aneurysm. It may rupture and lead to subarachnoid haemorrhage. Screening for cerebral aneurysm is recommended in young patients with a positive family history. The gene responsible for 85% of the cases (PKD1), has been identified in chromosome region 16p13. It covers 52kb and includes 46 exons giving a transcript of 14.5 kb coding for a protein of 4,203 amino acids, now called polycystin. Polycystin is probably an integral membrane protein with multiple extra-cellular domains that are involved in cell-cell and/or cell-matrix interactions. The gene accounting for the vast majority of the remaining cases (PKD2) has been identified in chromosome region 4q21. It codes for a protein of 968 amino acids, which appears to be a transmembrane protein, putatively functioning as an ion channel or pore. PKD1 could act as the regulator of PKD2 activity. ***Disruption*** of communication between matrix and cell by the mutated protein could account for the whole clinico-pathological features of ***ADPKD*** . Further understanding of both the function of PKD1 and PKD2 proteins and the cystic pathway should pave the way for therapeutic intervention.

L4 ANSWER 46 OF 56 CAPLUS COPYRIGHT 2003 ACS
AN 1996:627008 CAPLUS
DN 125:272691
TI Functional correction of renal defects in a mouse model for ARPKD through expression of the cloned wild-type Tg737 cDNA
AU Yoder, Bradley K.; Richards, William G.; Sommardahl, Carla; Sweeney, William E.; Michaud, Edward J.; Wilkinson, J. Erby; Avner, Ellis D.; Woychik, Richard P.
CS Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA
SO Kidney International (1996), 50(4), 1240-1248
CODEN: KDYIA5; ISSN: 0085-2538
PB Blackwell
DT Journal
LA English
AB Autosomal recessive polycystic kidney disease (ARPKD) is characterized by the formation of large collecting tubule and ductular cysts that often result in renal insufficiency within the first decade of life. Understanding the process leading to cyst formation will require the identification and characterization of genes involved in the etiol. of this disease. In this regard, the authors previously described the generation of a mouse model (TgN737Rpw) for ARPKD and the cloning of a candidate gene. Here, the authors show direct involvement of the Tg737 gene in collecting duct cyst formation by expressing the wild-type Tg737 cDNA as a ***transgene*** in TgN737Rpw mutants. In contrast to TgN737Rpw mutants, the "rescued" animals survive longer, have normal renal function and normal localization of the EGFr to the basolateral surfaces of collecting duct epithelium.

L4 ANSWER 47 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
29
AN 1996:508612 BIOSIS
DN PREV199699230968
TI Dysregulation of cellular proliferation and apoptosis mediates human autosomal dominant polycystic kidney disease (***ADPKD*** .
AU Lanoix, Jacqueline; D'Agati, Vivette; Szabolcs, Matthias; Trudel, Marie (1)
CS (1) 110 ouest ave. des Pins, Montreal, PQ H2W 1R7 Canada
SO Oncogene, (1996) Vol. 13, No. 6, pp. 1153-1160.
ISSN: 0950-9232.
DT Article
LA English
AB The proto-oncogene c-myc has been implicated in both cellular proliferation and apoptosis, and we have shown that overexpression of c-myc can induce polycystic kidney disease in ***transgenic*** mice. To elucidate the molecular and cellular defects underlying cystogenesis, we have investigated the potential roles of cell proliferation and apoptosis as they relate to c-myc and modulators of c-myc function in human autosomal dominant polycystic kidney disease (***ADPKD***). Renal c- myc expression was consistently elevated, up to 15-fold, in ***ADPKD*** . High levels of c-myc expression correlated with 10- to 100-fold increased proliferation index in cystic epithelium. Interestingly, steady-state levels of bcl-2 mRNA were also increased up to 20-fold and Bcl-2 protein was markedly elevated. In contrast, the expression of bax and p53 was virtually unchanged. However, apoptosis was

consistently and significantly increased in ***ADPKD*** kidneys, unchecked by high levels of Bcl-2. Together with proliferation, apoptosis may thus represent a general mechanism for cyst growth and tissue remodeling. We conclude that both epithelial cell proliferation and apoptosis required for normal kidney homeostasis are deregulated in ***ADPKD*** , recapitulating the renal developmental program. Furthermore, abnormal expression of proto-oncogenes regulating these processes is an important mediator of cystogenesis in human ***ADPKD***

L4 ANSWER 48 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
30
AN 1996:60347 BIOSIS
DN PREV199698632482
TI Screening the 3' region of the polycystic kidney disease 1 (PKD1) gene reveals six novel mutations.
AU Peral, Belen; San Millan, Jose L.; Ong, Albert C. M.; Gamble, Vicki; Ward, Christopher J.; Strong, Carol; Harris, Peter C. (1)
CS (1) MRC Mol. Haematol. Unit, Inst. Mol. Med., John Radcliffe Hosp., Headington, Oxford OX3 9DU UK
SO American Journal of Human Genetics, (1996) Vol. 58, No. 1, pp. 86-96. ISSN: 0002-9297.
DT Article
LA English
AB Recently, the gene for the most common form of autosomal dominant polycystic kidney disease (***ADPKD***), PKD1 (polycystic kidney disease 1), has been fully characterized and shown to encode an integral membrane protein, polycystin, involved in cell-cell and/or cell-matrix interactions. Study of the PKD1 gene has been complicated because most of the gene lies In a genomic region reiterated several times elsewhere on the same chromosome, and consequently only seven mutations have been described so far. Here we report a systematic screen covering apprx 80% of the apprx 2.75 kb of translated transcript that is encoded by single-copy DNA. We have identified and characterized six novel mutations that, together with the previously described changes, amount to a detection rate of 10%-15% in the population studied. The newly described mutations are two deletions, an insertion of a T-nucleotide causing a frameshift, two single-base-pair substitutions resulting in premature stop codons, and a G fwdarw C transversion that may be a missense mutation. These results have important implications for genetic diagnosis of PKD1 because they indicate that the majority of mutations lie within the duplicared area, which is difficult to study. The regions of polycystin removed in each mutation so far described are assessed for their functional significance; an area ***disrupted*** by two new small in-frame changes is highlighted. PKD1 mutations are contrasted with those in the PKD1/TSC2 contiguous-gene syndrome, and the likely mutational mechanism in PKD1 is considered.

L4 ANSWER 49 OF 56 CAPLUS COPYRIGHT 2003 ACS
AN 1995:851823 CAPLUS
DN 123:253655
TI Polycystic kidney disease 1 gene and uses for diagnosis and therapy
IN Harris, Peter Charles; Peral, Belen; Ward, Christopher James; Hughes, James; Breuning, Martin Hendrik; Peters, Dorothea Johanna Maria; Roelfsema, Jeroen Hendrik; Sampson, Julian; Halley, Dirkje Jorijntje Johanna; et al.
PA Medical Research Council, UK; Leiden Univ.; University of Wales College of Medicine; Erasmus University Rotterdam
SO PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9518225	A1	19950706	WO 1994-GB2822	19941223
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9513226	A1	19950717	AU 1995-13226	19941223
EP 736094	A1	19961009	EP 1995-904624	19941223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09507751	T2	19970812	JP 1994-517857	19941223
US 6485960	B1	20021126	US 1995-422582	19950414
WO 9534649	A2	19951221	WO 1995-GB1386	19950613
WO 9534649	A3	19960104		
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9528921	A1	19960105	AU 1995-28921	19950613
EP 777728	A1	19970611	EP 1995-924411	19950613
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 6207374	B1	20010327	US 1998-40738	19980318
US 6380360	B1	20020430	US 1998-52469	19980331
PRAI GB 1993-26470	A	19931224		
GB 1994-11900	A	19940614		
WO 1994-GB2822	W	19941223		
GB 1995-7766	A	19950413		
US 1995-422582	A	19950414		
WO 1995-GB1386	W	19950613		

AB Autosomal dominant polycystic kidney disease (***ADPKD***) is a common genetic disorder which frequently results in renal failure, due to progressive cyst development. The major locus, PKD1, maps to 16p13.3. A chromosome translocation is identified assocd. with ***ADPKD*** which ***disrupts*** a gene (PBP), encoding a 14 kb transcript, in the PKD1 candidate region. Further mutations of the PBP gene were found in PKD1 patients confirming that PBP is th PKD1 gene. This gene is located adjacent to the tuberous sclerosis (2) locus in a genomic region that is reiterated more proximally on 16p. The duplicate are encodes three transcripts substantially homologous to the PKD1 transcript. Partial sequence anal. of the PKD1 transcript shows that it encodes a novel protein. Screening of actual or suspected ***ADPKD*** patients for normal or mutated PKD1 can be used for diagnostic purposes. PKD-1 assocd. disorders such as ***ADPKD*** may be treated or prevented by PKD1 gene therapy and/or administration of functional PKD1 protein to affected cells.

L4 ANSWER 50 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 95349905 EMBASE
DN 1995349905
TI Polycystic kidney disease: Etiology, pathogenesis, and treatment.
AU Martinez J.R.; Grantham J.J.
CS Department of Medicine, University of Kansas Medical Center,Kansas City, KS, United States
SO Disease-a-Month, (1995) 41/11 (693-768).
ISSN: 0011-5029 CODEN: DIMOAN
CY United States
DT Journal; General Review
FS 028 Urology and Nephrology
LA English
SL English
AB Once viewed as hopelessly incurable disorders and the dustbin for careers in academic medicine, the polycystic kidney diseases have emerged as prime targets of pathophysiologic study and palliative and definitive treatment in the era of molecular medicine. Polycystic kidney disease (PKD) may be hereditary or acquired. The major inherited types are autosomal dominant (AD) and autosomal recessive (AR). ***ADPKD*** is caused by at least two (and possibly three) genes located on separate chromosomes, while ***ADPKD*** -1 is due to a 14 kb transcript in a duplicated region on the short arm of chromosome 16 very near the .alpha.-globin gene cluster and the gene for one form of tuberous sclerosis. ***ADPKD*** -2 has been assigned to the long arm of chromosome 4. ARPKD is due to a mutated gene on both copies of the long arm of chromosome 6. Cysts originate in renal tubules. Proliferation of tubule epithelial cells modulated by endocrine, paracrine, and autocrine factors is a major element in the pathogenesis of renal cystic diseases. In addition, fluid that is abnormally accumulated within the cysts is derived from glomerular filtrate and, to a greater extent, by transepithelial fluid secretion. Abnormal synthesis and degradation of matrix components associated with interstitial inflammation are additional features in the pathogenesis of renal cystic diseases. The ***ADPKD*** genotypes are characterized by bilateral kidney cysts, hypertension, hematuria, renal infection, stones, and renal insufficiency. ***ADPKD*** is a systemic disorder; cysts appear with decreasing frequency in the kidneys, liver, pancreas, brain, spleen, ovaries, and testis. Cardiac valvular disorders, abdominal and inguinal hernias, and aneurysms of cerebral and coronary arteries and aorta are also associated with ***ADPKD*** . Treatment is supportive: dietary regulation of salt and protein intake, control of hypertension and renal stones, and dialysis and transplantation at the end stage. ARPKD is a relatively rare disease that causes clinical symptoms at birth, with significant mortality in the first month of life. The cysts develop primarily in the collecting ducts because of a failure in the maturation process. Early complications include Potter's syndrome; excessive size of the kidneys, causing respiratory dysfunction; hypertension; and renal insufficiency. Hepatic fibrosis is an associated extrarenal problem that results in significant morbidity in young children and adolescents. Treatment includes supportive care, dialysis, and renal transplantation. Acquired cysts (solitary/simple) are commonplace in older persons. Multiple cysts may be seen in association with potassium ***deficiency*** , congenital disorders, metabolic diseases, and toxic renal injury. Acquired polycystic disease occurs in the setting of chronic, progressive renal scarring due to diabetes mellitus, chronic glomerulonephritis, or other renal disorders that lead to azotemia. Acquired cystic kidney disease (ACKD) is seen most commonly in patients undergoing dialysis (>75,000 cases) and is discovered incidentally in most instances. The nephrons that survive the underlying renal diseases are stimulated to grow and accumulate abnormal amounts of fluid. The disease is the consequence of the uremic environment, with replacement of renal function with an allograft leading to reversal of the cystic lesions in some cases. In contrast to patients with ***ADPKD*** and ARPKD, those with ACKD are more likely to have solitary or multicentric adenocarcinomas. Future therapies of hereditary renal cystic disorders will be directed at diminishing the extent of epithelial cellular proliferation, transepithelial fluid secretion, and interstitial fibrosis and at correcting the genetic defects.

L4 ANSWER 51 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
31

AN 1995:275466 BIOSIS
DN PREV199598289766
TI Splicing mutations of the polycystic kidney disease 1 (PKD1) gene induced by intronic deletion.
AU Peral, Belen; Gamble, Vicki; San Millan, Jose L.; Strong, Carol; Sloane-Stanley, Jackie; Moreno, Felipe; Harris, Peter C. (1)
CS (1) MRC Molecular Haematol. Unit, Inst. Molecular Med., John Radcliffe Hosp., Oxford, OX3 9DU UK
SO Human Molecular Genetics, (1995) Vol. 4, No. 4, pp. 569-574. ISSN: 0964-6906.
DT Article
LA English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) is a common genetic disease which frequently results in renal failure. The major ***ADPKD*** gene, polycystic kidney disease 1 (PKD1), has recently been identified. In an attempt to understand better the aetiology of this disorder we have searched for mutations in the PKD1 gene. Analysis of three regions in the 3' part of the gene has revealed two mutations that occur by a novel mechanism. Both mutations are deletions (of 18 or 20 bp) within the same 75 bp intron and although these deletions do not ***disrupt*** the splice donor or acceptor sites at the boundary of the intron, they nevertheless result in aberrant splicing. Two different transcripts are produced in each case; one includes the deleted intron while the other has a 66 bp deletion due to activation of a cryptic 5' splice site. No normal product is generated from the deleted gene. Aberrant splicing probably occurs because the deleted intron is too small for spliceosome assembly using the authentic splice sites; this mechanism has previously only been described from in vitro studies of vertebrate genes. A 9 bp direct repeat has been identified within the intron, which probably facilitated deletion by promoting misalignment of sequence. The possible phenotypic implications of producing more than one aberrant PKD1 transcript in these cases are discussed.

L4 ANSWER 52 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
32
AN 1994:358332 BIOSIS
DN PREV199497371332
TI The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16.
AU Ward, Christopher J.; Peral, Belen; Hughes, Jim; Thomas, Sandra; Gamble, Vicki; MacCarthy, Angela B.; Sloane-Stanley, Jackie; Buckle, Veronica J.; Kearney, Lyndal; et al.
CS Inq.: Peter C. Harris, Med. Res. Council Mol. Haematol. Unit, Inst. Radcliffe Hosp., Headington, Oxford OX3 9DU UK
SO Cell, (1994) Vol. 77, No. 6, pp. 881-894. ISSN: 0092-8674.
DT Article
LA English
AB Autosomal dominant polycystic kidney disease (***ADPKD***) is a common genetic disorder that frequently results in renal failure due to progressive cyst development. The major locus, PKD1, maps to 16p13.3. We identified a chromosome translocation associated with ***ADPKD*** that ***disrupts*** a gene (PBP) encoding a 14 kb transcript in the PKD1 candidate region. Further mutations of the PBP gene were found in PKD1 patients, two deletions (one a de novo event) and a splicing defect, confirming that PBP is the PKD1 gene. This gene is located adjacent to the TSC2 locus in a genomic region that is reiterated more proximally on 16p. The duplicate area encodes three transcripts substantially homologous to the PKD1 transcript. Partial sequence analysis of the PKD1 transcript shows that it encodes a novel protein whose function is at present unknown.

L4 ANSWER 53 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
33
AN 1995:63386 BIOSIS
DN PREV199598077686
TI Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease-A contiguous gene syndrome.
AU Brook-Carter, Phillip T.; Peral, Belen; Ward, Christopher J.; Thompson, Peter; Hughes, Jim; Maheshwar, Magitha M.; Nellist, Mark; Gamble, Vicki; Harris, Peter C.; Sampson, Julian R. (1)
CS (1) Inst. Med. Genetics, Univ. Wales Coll. Med., Cardiff CF4 4XN UK
SO Nature Genetics, (1994) Vol. 8, No. 4, pp. 328-332. ISSN: 1061-4036.
DT Article
LA English
AB Major genes which cause tuberous sclerosis (TSC) and autosomal dominant polycystic kidney disease (***ADPKD***), known as TSC2 and PKD1 respectively, lie immediately adjacent to each other on chromosome 16p. Renal cysts are often found in TSC, but a specific renal phenotype, distinguished by the severity and infantile presentation of the cystic changes, is seen in a small proportion of cases. We have identified large deletions ***disrupting*** TSC2 and PKD1 in each of six such cases studied. Analysis of the deletions indicates that they inactivate PKD1, in contrast to the mutations reported in ***ADPKD*** patients, where in each case abnormal transcripts have been detected.

L4 ANSWER 54 OF 56 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
34
AN 1991:279323 BIOSIS
DN BA92:11938
TI C-MYC AS AN INDUCER OF POLYCYSTIC KIDNEY DISEASE IN ***TRANSGENIC***
MICE.
AU TRUDEL M; D'AGATI V; COSTANTINI F
CS INST. RECH. CLINIQUES MONTREAL, 110 OUEST AVE. DES PINS, MONTREAL, QUEBEC,
CAN. H2W 1R7.
SO KIDNEY INT, (1991) 39 (4), 665-671.
CODEN: KDYIA5. ISSN: 0085-2538.
FS BA; OLD
LA English
AB In this study, a genetic model of polycystic kidney disease (PKD) has been produced in ***transgenic*** mice bearing the murine c-myc gene driven by the SV40 enhancer and the adult .beta.-globin promoter. These animals reproducibly develop PKD and die of renal failure. The phenotype appears to result from the overexpression of c-myc in the renal tubular epithelium and consequent abnormal cell proliferation. These ***transgenic*** mice represent a genetic model of PKD which bears similarities to human autosomal dominant PKD (***ADPKD***) with respect to renal morphology, renal functional alterations and dominant transmission. Study of these ***transgenic*** mice may offer valuable insights into the pathogenesis of PKD.

L4 ANSWER 55 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 90020477 EMBASE
DN 1990020477
TI Liver cysts associated with polycystic kidney disease: Role of Tc-99m hepatobiliary imaging.
AU Salam M.; Keeffe E.B.
CS Division of Gastroenterology, Oregon Health Sciences University, 3181 S.W.Sam Jackson Park Road, Portland, OR 97201, United States
SO Clinical Nuclear Medicine, (1989) 14/11 (803-807). ISSN: 0363-9762 CODEN: CNMEDK
CY United States
DT Journal; Article
FS 014 Radiology
022 Human Genetics
023 Nuclear Medicine
028 Urology and Nephrology
048 Gastroenterology
037 Drug Literature Index
LA English
SL English
AB A 42-year-old woman with multiple hepatic cysts associated with ***autosomal*** ***polycystic*** ***kidney*** ***disease*** was evaluated for abdominal discomfort and new liver test abnormalities following blind aspirations of her liver cysts. Tc-99m mebrofenin hepatobiliary imaging revealed a markedly enlarged liver with multiple photon ***deficient*** areas, focal retention of isotope in the left hepatic ductal system, no accumulation of radionuclide in cysts, and an unusual medial gallbladder position. Endoscopic retrograde cholangiography confirmed all of these findings. Abdominal discomfort and liver biochemical abnormalities were attributed to cyst compression of nearby structures, including bile ducts. Hepatobiliary imaging is useful to exclude communication of bile ducts with hepatic cysts, to detect incidental abnormalities such as partial bile duct obstruction, and to distinguish the gallbladder from nearby hepatic cysts.

L4 ANSWER 56 OF 56 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 89076981 EMBASE
DN 1989076981
TI Hyperuricemia, gout, and autosomal dominant polycystic kidney disease.
AU Mejias E.; Navas J.; Lluberes R.; Martinez-Maldonado M.
CS Department of Internal Medicine, San Juan Veterans Administration Medical Center, San Juan 00927-5800, Puerto Rico
SO American Journal of the Medical Sciences, (1989) 297/3 (145-148). ISSN: 0002-9629 CODEN: AJMSA
CY United States
DT Journal
FS 006 Internal Medicine
022 Human Genetics
028 Urology and Nephrology
029 Clinical Biochemistry
031 Arthritis and Rheumatism
LA English
SL English
AB The relationship between hyperuricemia, gout, and autosomal dominant polycystic kidney disease (***ADPKD***) is not widely recognized. In an attempt to further clarify this relationship, the authors have studied 17 patients with ***ADPKD*** , 9 controls, 9 patients with proven gout and chronic renal failure, 11 patients with gout and normal renal function, and 11 patients with chronic renal failure. The mean serum uric acid concentration was higher in patients with ***ADPKD*** as a group than in controls (8.0 .+-. 1.7 mg/dl vs. 6.4 .+-. 1.6 mg/dl, $p < .02$). Clinical gout was identified in 24% of patients with ***ADPKD*** ; none of the patients with chronic renal failure of other etiologies had gout. Fractional excretion of uric acid and the activity of the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) were not different among the groups studied. From this study the authors conclude that ***ADPKD*** should be included among those diseases associated with hyperuricemia and gout. A partial ***deficiency*** in HGPRT or abnormal renal handling of uric acid do not appear to be responsible for

the increased incidence of gout in patients with ***ADPKD*** .

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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		147.34	147.55

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	ENTRY	SINCE FILE SESSION	TOTAL
CA SUBSCRIBER PRICE		-3.26	-3.26

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